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FILE COVERS 1907 - 17 Mar 2003 VOL 138 ISS 12
FILE LAST UPDATED: 16 Mar 2003 (20030316/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot l71

L71 ANSWER 1 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:688469 HCAPLUS
DN 137:215809
TI Non-myeloablative **tolerogenic** treatment
IN Slavin, Shimon; Prigozhina, Tatyana
PA Hadasit Medical Research Services and Development Ltd., Israel
SO U.S., 52 pp., Cont.-in-part of U.S. 6,428,782.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K038-00
ICS A61K048-00; C12N015-85
NCL 424093100
CC 15-2 (Immunochemistry)
Section cross-reference(s): 1, 14
FAN.CNT 4

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	US 6447767	B1	20020910		US 2000-506082	20000216	<--
	US 6428782	B1	20020806		US 1998-222011	19981231	<--
PRAI	US 1997-862550	B2	19970523	<--			
	US 1998-222011	A2	19981231	<--			

AB The present invention features a method of inducing donor-specific tolerance in a host. **Tolerogenic** treatments of the present invention may be administered to a host prior to transplantation of donor-derived materials. The **tolerogenic** treatment involves (1) administering an immunosuppressive agent to a host mammal in a non-myeloablative regimen sufficient to decrease, but not necessarily to eliminate, the host mammal's functional T lymphocyte population; (2) infusing donor antigens from a non-syngeneic donor into the host mammal; (3) eliminating those host T lymphocytes responding to the infused donor antigens using a non-myeloablative dose of lymphocytotoxic or tolerizing agent; and (4) administering donor **hematopoietic** cells to the host mammal. Donor lymphoid cells used for cell therapy of a host mammal can be depleted of host specific immunol. reactivity by methods essentially similar to those use for tolerizing a host mammal prior to transplantation.

ST cancer allotransplant tolerance **radiotherapy** lymphocyte

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HLA (human leukocyte-assocd. antigen); non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)

IT Antigens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alloantigens; non-myeloablative **tolerogenic** treatment of cancer)

IT Erythrocyte
(allogeneic; non-myeloablative **tolerogenic** treatment of cancer)

IT **Transplant and Transplantation**
(allotransplant, **bone marrow**; non-myeloablative **tolerogenic** treatment of cancer)

IT **Transplant and Transplantation**
(allotransplant, heart; non-myeloablative **tolerogenic** treatment of cancer)

IT **Transplant and Transplantation**
(allotransplant, skin; non-myeloablative **tolerogenic** treatment of cancer)

IT **Bone marrow**
Heart
Skin
(allotransplant; non-myeloablative **tolerogenic** treatment of cancer)

IT **Transplant rejection**
(allotransplant; non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)

IT Leukemia
(chronic myelocytic; non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)

IT Neuroglia
(glioblastoma; non-myeloablative **tolerogenic** treatment of cancer)

IT **Transplant and Transplantation**
(graft-vs.-host reaction; non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)

IT Digestive tract
Urinary tract
(neoplasm; non-myeloablative **tolerogenic** treatment of cancer)

IT Antitumor agents
Bone marrow
Brain, neoplasm
Human
Immune tolerance
Immunosuppression
Immunotherapy
Kidney, neoplasm
Leukemia
Lung, neoplasm
Lymphocyte
Lymphoma
Melanoma
Neoplasm
Nerve, neoplasm

T cell (lymphocyte)
(non-myeloablative **tolerogenic** treatment of cancer)
IT Adoptive immunotherapy
Radiotherapy
(non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)
IT CD20 (antigen)
Carcinoembryonic antigen
Interleukin 4
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)
IT Interleukin 2
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)
IT 50-18-0, Cyclophosphamide 21679-14-1, Fludarabine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-myeloablative **tolerogenic** treatment of cancer)
IT 84210-80-0, ASTA-Z 7557 156586-89-9, Panorex
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-myeloablative **tolerogenic** treatment of cancer and prevention of allograft rejection)
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
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(1) Anon; WO 9313785 1993 HCAPLUS
(2) Anon; WO 9409803 1994 HCAPLUS
(3) Anon; WO 9503062 1995 HCAPLUS
(4) Anon; WO 9637208 1996 HCAPLUS
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(8) Boyer; Blood 1997, V89(9), P3477 HCAPLUS
(9) Colson; J Immunology 1995, V155, P4179 HCAPLUS
(10) Eto; J Urology 1995, V153, P1693 MEDLINE
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(14) Idstad; US 5635156 A 1997 HCAPLUS
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(17) Knobler; Transplantation 1985, V40(2), P223 MEDLINE
(18) Korngold; Transplantation 1994, V58(3), P278 MEDLINE
(19) Kwak; Lancet 1995, V345, P1016 MEDLINE
(20) Latinne; Transplantation 1994, V57(2), P238 MEDLINE
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L71 ANSWER 2 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:587644 HCAPLUS

DN 137:139380
TI Non-myeloablative **tolerogenic** treatment
IN Slavin, Shimon; Prigozhina, Tatyana
PA Hadasit Medical Research Services and Development Ltd., Israel
SO U.S., 46 pp., Cont.-in-part of U.S. Ser. No. 862,550, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K038-00
ICS C12N005-08
NCL 424093100
CC 15-8 (Immunochemistry)
Section cross-reference(s): 1, **8**
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 6428782	B1	20020806	US 1998-222011	19981231	<--
	CA 2356434	AA	20000713	CA 1999-2356434	19991223	<--
	WO 2000040701	A2	20000713	WO 1999-US30704	19991223	<--
	WO 2000040701	A3	20001221			
	W: CA, IL, JP, MX					
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	EP 1141246	A2	20011010	EP 1999-968946	19991223	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	JP 2002534083	T2	20021015	JP 2000-592399	19991223	<--
	US 6447767	B1	20020910	US 2000-506082	20000216	<--
PRAI	US 1997-862550	B2	19970523	<--		
	US 1998-222011	A	19981231	<--		
	WO 1999-US30704	W	19991223			

AB The present invention features a method of inducing donor-specific tolerance in a host. **Tolerogenic** treatments of the present invention may be administered to a host prior to transplantation of donor-derived materials. The **tolerogenic** treatment involves (1) administering an immunosuppressive agent to a host mammal in a non-myeloablative regimen sufficient to decrease, but not necessarily to eliminate, the host mammal's functional T lymphocyte population; (2) infusing donor antigens from a non-syngeneic donor into the host mammal; (3) eliminating those host T lymphocytes responding to the infused donor antigens using a non-myeloablative dose of lymphocytotoxic or tolerizing agent; and (4) administering donor **hematopoietic** cells to the host mammal. Donor lymphoid cells used for cell therapy of a host mammal can be depleted of host specific immunol. reactivity by methods essentially similar to those use for tolerizing a host mammal prior to transplantation.

ST transplant tolerance allograft immunosuppressant immunotherapy
IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HLA (human leukocyte-assocd. antigen); procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)
IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex); procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)
IT Antigens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alloantigens; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)
IT **Transplant and Transplantation**

(allotransplant, **bone marrow**; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Transplant and Transplantation**
(allotransplant, heart; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Transplant and Transplantation**
(allotransplant, skin; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Bone marrow**
Heart
Skin
Transplant and Transplantation
Transplant rejection
(allotransplant; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Leukemia
(chronic myelocytic; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Transplant and Transplantation**
(graft-vs.-host reaction; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(minor; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Lymphocyte
(natural killer cell; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Adoptive immunotherapy
Antitumor agents
Bone marrow
Hematopoietic precursor cell
Hodgkin's disease
Human
Immune tolerance
Immunosuppressants
Immunosuppression
Immunotherapy
Lymphocyte
Mammalia
Radiotherapy
T cell (lymphocyte)
(procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Interleukin 2
Interleukin 4
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Transplant and Transplantation**
(skin, xenotransplant; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Skin
(transplant, xenotransplant; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Antibodies
RL: REM (Removal or disposal); PROC (Process)
(xenoantibodies; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Antigens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(xenoantigens; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Transplant rejection**
(xenograft; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT **Transplant and Transplantation**
(xenotransplant; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

IT 50-18-0, Cyclophosphamide 88859-04-5, Mafosfamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(procedure for the non-myeloablative **tolerogenic** prevention of allograft or xenograft rejection)

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L71 ANSWER 3 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **2001:751262** HCAPLUS
DN **137:373**
TI A new method for tolerance induction: Busulfan administration followed by intravenous injection of neuraminidase-treated donor **bone marrow**
AU Nagahama, Takashi; **Sugiura, Kikuya**; Lee, Shinryu; **Morita, Haruo**; Adachi, Yasushi; Kwon, A-Hon; Kamiyama, Yasuo; **Ikehara, Susumu**
CS The First Department of Pathology, Kansai Medical University, Osaka, 570-8506, Japan
SO Stem Cells (Miamisburg, OH, United States) (2001), 19(5), 425-435
CODEN: STCEEJ; ISSN: 1066-5099
PB AlphaMed Press
DT Journal
LA English
CC 1-7 (Pharmacology)
Section cross-reference(s): 15
AB The portal venous (p.v.) administration of foreign cells induces donor-specific tolerance. Recently, it was demonstrated that the p.v. administration of donor cells elicits donor-specific tolerance across major histocompatibility complex barriers. The present study utilized the intrahepatic tolerance-inducing system to establish a new method for organ transplantation: use of both busulfan ([Bu] to provide a sufficient "space" for the donor hematopoietic cells to expand in the recipient) and neuraminidase ([Neu] to enhance the trapping of i.v. injected cells in the liver). **Radiolabeled bone marrow** cells (BMCs) exclusively accumulated in the livers of recipient mice as a result of Neu treatment. Furthermore, hematopoietic progenitors (forming hematopoietic foci) in the accumulated BMCs were retained in the recipient livers for >18 days. C57BL/6 (B6) mice that had been transplanted with skins of BALB/c mice immediately after the injection of BALB/c BMCs showed a 90% skin graft survival rate over 400 days as a result of using the combination of injecting 50 mg Bu/kg into the B6 mice and treatment of the BALB/c BMCs with 0.25 U Neu/mL. However, the survival rate decreased when either the Bu or Neu treatment was omitted. In tolerant recipients, microchimerism was obsd. in the various hematolymphoid organs. T cells collected from the tolerant recipients suppressed proliferative responses

to the donor alloantigens but enhanced the prodn. of Th2 and Th3 cytokines. These findings suggest that the enhanced retention of donor BMCs in the recipient livers as a result of the Bu and Neu treatments efficiently induces tolerance. Therefore, this "single-day protocol" would be of great advantage for human organ transplantation.

ST organ transplant tolerance busulfan neuraminidase **bone marrow**

IT **Bone marrow**
Transplant and Transplantation
(busulfan administration followed by i.v. injection of neuraminidase-treated donor **bone marrow** induces tolerance to organ transplants)

IT Hematopoietic precursor cell
(busulfan administration followed by i.v. injection of neuraminidase-treated donor **bone marrow** induces tolerance to organ transplants in relation to liver accumulation of)

IT Liver
(busulfan administration followed by i.v. injection of neuraminidase-treated donor **bone marrow** induces tolerance to organ transplants in relation to liver accumulation of hematopoietic precursor cells)

IT **Transplant and Transplantation**
(skin; busulfan administration followed by i.v. injection of neuraminidase-treated donor **bone marrow** induces tolerance to organ transplants)

IT Skin
(transplant; busulfan administration followed by i.v. injection of neuraminidase-treated donor **bone marrow** induces tolerance to organ transplants)

IT 55-98-1, Busulfan 9001-67-6, Neuraminidase
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(busulfan administration followed by i.v. injection of neuraminidase-treated donor **bone marrow** induces tolerance to organ transplants)

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L71 ANSWER 4 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **2001:379909** HCAPLUS
DN **135:151488**
TI Intra-**bone marrow** injection of allogeneic **bone marrow** cells: a powerful new strategy for treatment of intractable autoimmune diseases in MRL/lpr mice
AU Kushioa, Taketoshi; Inaba, Muneo; Hisha, Hiroko; Ichioka, Naoya; Esumi, Takashi; Ogawa, Flyokei; Iida, Hirokazu; **Ikehara, Susumu**
CS First Department of Pathology, Transplantation Center, Kansai Medical University, Moriguchi City, 570-8506, Japan
SO Blood (2001), 97(10), 3292-3299
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB Intractable autoimmune diseases in chimeric resistant MRL/lpr mice were treated by a new **bone marrow** transplantation (BMT) method consisting of fractionated **irradn.**, 5.5 Gy .times. 2, followed by intrabone marrow (IBM) injection of whole **bone marrow** cells (BMCs) from allogeneic normal C57BL/6 (B6) mice (5.5 Gy .times. 2 + IBM). In MRL/lpr mice treated with this method, the no. of donor-derived cells in the **bone marrow**, spleen, and liver rapidly increased (almost 100% donor-derived cells by 14 days after the treatment), and the no. of donor-derived hemopoietic progenitor cells concomitantly increased. Furthermore, donor-derived stromal cells were clearly detected in the cultured bone pieces from MRL/lpr mice treated with 5.5 Gy .times. 2 + IBM. All the recipients thus treated survived more than 1 yr (> 60 wk after birth) and remained free from autoimmune diseases. Autoantibodies decreased to almost normal levels, and abnormal T cells (Thy1.2+/B220+/CD4-/CD8-) disappeared. Hematolymphoid cells were reconstituted with donor-derived cells, and newly developed T cells were tolerant to both donor (B6)-type and host (MRL/lpr)-type major histocompatibility complex determinants. Successful cooperation was achieved among T cells, B cells, and antigen-presenting cells when evaluated by in vitro antisheep red blood cell responses. These findings clearly indicate that this new strategy (IBM-BMT) creates the appropriate hemopoietic environment for the early recovery of hemopoiesis and donor cell engraftment, resulting in the complete amelioration of intractable autoimmune diseases in chimeric resistant MRL/lpr mice without recourse to immunosuppressants. This strategy would therefore be suitable for human therapy.
ST intra **bone marrow** transplant autoimmune disease treatment autoantibody
IT Antibodies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(autoantibodies; intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice and decrease of)

IT **Transplant and Transplantation**
(**bone marrow**; intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice)

IT Autoimmune disease
Hematopoiesis
Hematopoietic precursor cell
(intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice)

IT Gamma ray
(intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice and decrease of)

IT **Immunosuppressants**
(intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice without)

IT Cell
(stem; intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice)

IT **Bone marrow**
(stroma; intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice)

IT **Bone marrow**
(transplant; intra-**bone marrow** injection of allogeneic **bone marrow** cells: for treatment of intractable autoimmune diseases in MRL/lpr mice)

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L71 ANSWER 5 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:282388 HCAPLUS
DN 135:60111
TI UVB-**irradiated** dendritic cells are impaired in their APC function and tolerize primed Th1 cells but not naive CD4+ T cells
AU Denfeld, Ralf W.; Hara, Hisamichi; Tesmann, Jens P.; Martin, Stefan; Simon, Jan C.
CS Department of Dermatology, Albert-Ludwigs-Universitat, Freiburg, 79104, Germany
SO Journal of Leukocyte Biology (2001), 69(4), 548-554
CODEN: JLBIE7; ISSN: 0741-5400
PB Federation of American Societies for Experimental Biology
DT Journal
LA English
CC 15-10 (Immunochemistry)
AB We have shown that low-dose UVB **radiation** converts Langerhans cells (LC) from immunogenic to **tolerogenic** APC. Therefore, we questioned whether low-dose UVB **irradn.** of **bone marrow**-derived dendritic cells (DC) alters their APC function, thereby inducing tolerance in T cells. To address this issue, cocultures of DC; and naive, allogeneic T cells; naive, OVA-specific TCR-transgenic T cells from DO11.10 mice; or primed, antigen-specific T cells using the Th1 clone AE7 were analyzed. First, we found low-dose UVB-**irradiated** DC (UVB-DC) to dose-dependently (50-200 J/M2) inhibit T-cell proliferation of naive and primed T cells. In addn., supernatants harvested from cocultures of UVB-DC and naive T cells showed markedly reduced levels of IL-2 and IFN-.gamma. and to a lesser degree of IL-4 and IL-10, suggesting a preferential down-regulation of Th1 responses by UVB-DC. FACS anal. of UVB-DC revealed no changes in surface expression of MHC, costimulatory, and adhesion mols. To test tolerance induction, allo- or antigen-specific T cells isolated from cocultures with **unirradiated** DC and UVB-DC were restimulated with **unirradiated** DC or IL-2. It is interesting that UVB-DC induced antigen-specific tolerance in the Th1 clone AE7. In contrast, UVB-DC induced a partial inhibition of allogeneic T-cell proliferation but no tolerance with similar unresponsiveness to restimulation with IL-2 and **unirradiated** DC irresp. of their haplotype. Similar observations were made when naive, TCR-transgenic T cells from DO11.10 mice were used. In conclusion, UVB-DC are impaired in their APC function and tolerize the primed antigen-specific Th1 clone AE7 but not naive allo- or OVA-specific T cells.
ST UVB **radiation** dendritic cell antigen presentation cytokine tolerance lymphocyte

IT Antigen presentation
CD4-positive T cell
Dendritic cell
Immune tolerance
UV B radiation
(UVB **irradiated** dendritic cells impaired in antigen presentation and cytokine prodn. and inducing tolerance in primed Th1 but not naive CD4+ T cells)
IT Interleukin 10
Interleukin 2
Interleukin 4
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(UVB **irradiated** dendritic cells impaired in antigen presentation and cytokine prodn. and inducing tolerance in primed Th1 but not naive CD4+ T cells)
IT T cell (lymphocyte)
(helper cell/inducer, TH1; UVB **irradiated** dendritic cells impaired in antigen presentation and cytokine prodn. and inducing tolerance in primed Th1 but not naive CD4+ T cells)
IT T cell (lymphocyte)
(proliferation; UVB **irradiated** dendritic cells impaired in antigen presentation and cytokine prodn. and inducing tolerance in primed Th1 but not naive CD4+ T cells)
IT Interferons
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(.gamma.; UVB **irradiated** dendritic cells impaired in antigen presentation and cytokine prodn. and inducing tolerance in primed Th1 but not naive CD4+ T cells)
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L71 ANSWER 6 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:825822 HCAPLUS
DN 134:114806
TI Mechanisms of tolerance induction by a gene-transferred peptide-IgG fusion

protein expressed in B lineage cells

AU El-Amine, Moustapha; Melo, Marco; Kang, Yubin; Nguyen, Hao; Qian, Jiahua; Scott, David W.
CS Department of Immunology, American Red Cross, J. Holland Laboratory, Rockville, MD, 20855, USA

SO Journal of Immunology (2000), 165(10), 5631-5636
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
CC 15-10 (Immunochemistry)

AB A gene therapy model has been designed to induce tolerance to multiple epitopes expressed in-frame on a sol. IgG fusion protein scaffold. Tolerance to the .lambda. repressor cI sequence p1-102 or its immunodominant epitopes (p12-26, p73-88) can be elicited when **bone marrow** (BM) or LPS blasts are transduced and injected into naive or even primed recipients. To explore the mechanism of tolerance, class II-/- (knockout, KO) BM cells were transduced with p1-102-IgG and transferred to **irradiated** recipients. These cells failed to induce tolerance to challenge with p1-102 epitopes, whereas transduced +/+ BM cells did. This supports the importance of class II MHC on the **tolerogenic** APC rather than secretion and representation in **tolerogenesis**. When BM cells from .mu.MT KO mice were transfected with p12-26-IgG and injected into **irradiated** mice, these transduced BM cells also failed to induce tolerance to an immunodominant epitope. These results suggest the direct involvement of B cells in tolerance to p1-102 epitopes. IL-10 KO BM cells infected with a p12-26-IgG construct were still **tolerogenic**. Importantly, anti-CTLA-4 injections reversed tolerance in primed, but not in naive, recipients of transduced LPS blasts. These data emphasize the importance of MHC class II presentation, B cell involvement, and CTLA-4 engagement in induction and/or maintenance of tolerance.

ST tolerance transgene IgG fusion protein B cell

IT Immunoglobulins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(G1, fusion products, with peptide epitope; mechanisms of tolerance induction by IgG fusion protein transgene expressed in B lineage cells)

IT Histocompatibility antigens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex), class II; expression by B lineage cells is required for **tolerogenesis** to IgG fusion protein)

IT B cell (lymphocyte)
(accessory cell; mechanisms of tolerance induction by IgG fusion protein transgene expressed in)

IT Antigen presentation
Immune tolerance
(mechanisms of tolerance induction by IgG fusion protein transgene expressed in B lineage cells)

IT Fusion proteins (chimeric proteins)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(mechanisms of tolerance induction by IgG fusion protein transgene expressed in B lineage cells)

IT Gene therapy
(mechanisms of tolerance induction by IgG fusion protein transgene expressed in B lineage cells in relation to)

IT Epitopes
(mechanisms of **tolerogenesis** by B-cells secreting chimeric IgG with expression of)

IT CTLA-4 (antigen)

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(regulation of tolerance induction by IgG fusion protein transgene expressed in B lineage cells)

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L71 ANSWER 7 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:475773 HCAPLUS
DN 133:84267
TI Non-myeloablative **tolerogenic** treatment
IN Slavin, Shimon; Prigozhina, Tatyana
PA Hadasit Medical Research Services and Developent Ltd., Israel; Baxter International Inc.
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N005-08
ICS A61K035-12; A61K035-28; A61K039-00; A61P037-02
CC 1-7 (Pharmacology)
Section cross-reference(s): 15
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040701	A2	20000713	WO 1999-US30704	19991223 <--
	WO 2000040701	A3	20001221		
	W: CA, IL, JP, MX				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6428782	B1	20020806	US 1998-222011	19981231 <--
	CA 2356434	AA	20000713	CA 1999-2356434	19991223 <--
	EP 1141246	A2	20011010	EP 1999-968946	19991223 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002534083	T2	20021015	JP 2000-592399	19991223 <--
PRAI	US 1998-222011	A	19981231 <--		

US 1997-862550 B2 19970523 <--
WO 1999-US30704 W 19991223

AB The present invention features a method of inducing donor-specific tolerance in a host. **Tolerogenic** treatments of the present invention may be administered to a host prior to transplantation of donor-derived materials. The **tolerogenic** treatment involves (1) administering an immunosuppressive agent to a host mammal in a non-myeloablative regimen sufficient to decrease, but not necessarily to eliminate, the host mammal's functional T lymphocyte population; (2) infusing donor antigens from a non-syngeneic donor into the host mammal; (3) eliminating those host T lymphocytes responding to the infused donor antigens using a non-myeloablative dose of lymphocytotoxic or tolerizing agent; and (4) administering donor **hematopoietic** cells to the host mammal. Donor lymphoid cells used for cell therapy of a host mammal can be depleted of host specific immunol. reactivity by methods essentially similar to those used for tolerizing a host mammal prior to transplantation.

ST immune tolerance induction donor antigen immunosuppressant; T lymphocyte elimination immunosuppressant immune tolerance; transplantation immune tolerance induction immunosuppressant

IT **Transplant and Transplantation**
Transplant and Transplantation
(**bone marrow**, induction of immune tolerance to recipient in, graft-vs.-host disease prevention in relation to; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT Antigens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(donor; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT **Transplant and Transplantation**
(graft-vs.-host reaction, prevention of by immune tolerance induction; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT T cell (lymphocyte)
(immune tolerance induction in; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT Leukemia
Neoplasm
(immunotherapy of, immune tolerance induction to prevent graft-vs.-host disease in; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT **Immune tolerance**
Immunosuppressants
Transplant and Transplantation
Transplant rejection
(non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT Immunotherapy
(of leukemia, immune tolerance induction to prevent graft-vs.-host disease in; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT Cytokines
Interleukin 10
Interleukin 2
Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(prodn. in immunotherapy of leukemia, graft-vs.-host disease prevention in relation to; non-myeloablative induction of tolerance using donor

antigens and immunosuppressants to prevent transplantation rejection)

IT **Hematopoietic precursor cell**
(stem, in immune tolerance induction; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to T lymphocytes, in immune tolerance induction; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT **Bone marrow**
Bone marrow
(transplant, induction of immune tolerance to recipient in, graft-vs.-host disease prevention in relation to; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT **Radiotherapy**
(x-ray, T lymphocyte depletion with, in immune tolerance induction; non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

IT 50-18-0, Cyclophosphamide 21679-14-1, Fludarabine 88859-04-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-myeloablative induction of tolerance using donor antigens and immunosuppressants to prevent transplantation rejection)

L71 ANSWER 8 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:291543 HCAPLUS
DN 133:57281
TI Donor MHC class II antigen is essential for induction of transplantation tolerance by **bone marrow** cells
AU Umemura, Akihisa; Monaco, Anthony P.; Maki, Takashi
CS Transplant Center, Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA
SO Journal of Immunology (2000), 164(9), 4452-4457
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB Post-transplant infusion of donor **bone marrow** cells (BMC) induces tolerance to allografts in adult mice, dogs, nonhuman primates, and probably humans. Here the authors used a mouse skin allograft model and an allogeneic **radiation** chimera model to examine the role of MHC Ags in tolerance induction. Infusion of MHC class II Ag-deficient (CIID) BMC failed to prolong C57BL/6 (B6) skin grafts in ALS- and rapamycin-treated B10.A mice, whereas wild-type B6 or MHC class I Ag-deficient BMC induced prolongation. Removal of class II Ag-bearing cells from donor BMC markedly reduced the **tolerogenic** effect compared with untreated BMC, although graft survival was significantly longer in mice given depleted BMC than that in control mice given no BMC. Infusion of CIID BMC into **irradiated** syngeneic B6 or allogeneic B10.A mice produced normal lymphoid cell reconstitution including CD4+ T cells except for the absence of class II Ag-pos. cells. However, **irradiated** B10.A mice reconstituted with CIID BMC rejected all B6 and a majority of CIID skin grafts despite continued maintenance of high degree chimerism. B10.A mice reconstituted with B6 BMC maintained chimerism and accepted both B6 and CIID skin grafts. Thus, expression of MHC class II Ag on BMC is essential for allograft tolerance induction and peripheral chimerism with cells deficient in class II Ag does not

guarantee allograft acceptance.
ST MHC class II allograft tolerance **bone marrow**
IT Histocompatibility antigens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(I-Ab; donor MHC class II antigen is essential for induction of allograft tolerance by post-transplant **bone marrow** cells)
IT **Transplant and Transplantation**
Transplant and Transplantation
(allotransplant, skin; donor MHC class II antigen is essential for induction of allograft tolerance by post-transplant **bone marrow** cells)
IT Skin
Transplant rejection
(allotransplant; donor MHC class II antigen is essential for induction of allograft tolerance by post-transplant **bone marrow** cells)
IT **Bone marrow**
Immune tolerance
(donor MHC class II antigen is essential for induction of allograft tolerance by post-transplant **bone marrow** cells)
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L71 ANSWER 9 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1999:789699** HCAPLUS

DN **132:22167**
TI Hematopoietic stem cell preparations for transplantation
IN **Ikehara, Susumu**; Inaba, Muneo; Takeuchi, Kenji; Kushida, Taketoshi
PA Ohtsuka Pharmaceutical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K035-28
ICS A61K031-00; A61K035-14
CC 15-1 (Immunochemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 11343242	A2	19991214	JP 1999-58942	19990305 <--
	US 6383481	B1	20020507	US 1999-265418	19990310 <--
PRAI	JP 1998-84275	A	19980330 <--		

AB The prepns. are intraportally injected to patients who have previously undergone **irradn.** to treat not only hematol. diseases, e.g. chronic myelocytic leukemia, acute myelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndrome, etc., but also autoimmune diseases. I.v. injection may be further performed after intraportal administration. The method prevents incomplete graft survival/graft rejection and eliminates the need for long-term used of immunosuppressants. **Bone marrow** cells collected from a donor mouse were incubated with anti-Thy-1.2 monoclonal antibody to remove T cells and mixed with rabbit serum as a source of complements. The cell suspension was intraportally injected to recipient mice (MRL/lpr) developing autoimmune disease, which had received total body **irradn.** with .gamma.-ray at 5.5 Gy 2 times. After 5 days, the cell suspension was i.v. injected to the recipients. Survival rates 25 wk after the treatment was 100%.

ST hematopoietic stem cell transplantation portal vein rejection prevention; **bone marrow** transplantation portal vein survival increase

IT **Transplant and Transplantation**
Transplant and Transplantation
(allotransplant, **bone marrow**; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

IT **Bone marrow**
(allotransplant; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

IT Blood
(disease; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

IT Gamma ray
(**irradn.**; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

IT Vein
(portal; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

IT Hematopoietic precursor cell
(stem; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

IT Autoimmune disease
(treatment of; transplantation of hematopoietic stem cells by intraportal administration to prevent incomplete survival/graft rejection)

L71 ANSWER 10 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:789029 HCAPLUS
DN 130:24094
TI Non-myeloablative **tolerogenic** treatment
IN Slavin, Shimon; Prigozhina, Tatyana
PA Hadasit Medical Research Services and Development, Israel; Baxter International Inc.
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K035-00
CC 15-1 (Immunochemistry)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9852582	A2	19981126	WO 1998-US10575	19980522 <--
	WO 9852582	A3	19990225		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9877981	A1	19981211	AU 1998-77981	19980522 <--
	EP 983074	A2	20000308	EP 1998-926059	19980522 <--
	R: BE, DE, FR, GB, IT				
	JP 2002502377	T2	20020122	JP 1998-550717	19980522 <--
PRAI	US 1997-862550	A	19970523 <--		
	WO 1998-US10575	W	19980522 <--		

AB The present invention features a method of inducing donor-specific tolerance in a host. **Tolerogenic** treatments of the present invention may be administered to a host prior to transplantation of donor-derived materials. The **tolerogenic** treatment involves (1) administering an immunosuppressive agent to a host mammal in a non-myeloablative regimen sufficient to decrease, but not necessarily to eliminate, the host mammal's functional T lymphocyte population; (2) infusing donor antigens from a non-syngeneic donor into the host mammal; (3) eliminating those host T lymphocytes responding to the infused donor antigens using a non-myeloablative dose of lymphocytotoxic or tolerizing agent; and (4) administering donor **hematopoietic** cells to the host mammal.

ST immune tolerance immunosuppressant T lymphocyte depletion; allograft xenograft tolerance **hematopoietic** stem cell

IT **Transplant and Transplantation**
(allotransplant; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT **Transplant and Transplantation**
(**bone marrow**; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Spleen
(cell transplant; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Metabolism, animal
(disorder; method for inducing tolerance comprises administration of

donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Enzymes, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(disorders; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Disease, animal
(enzyme-related; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT **Transplant and Transplantation**
(heart; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Cytotoxic agents
(lympho-; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Adoptive immunotherapy
Alkylating agents, biological
Antitumor agents
Blood
Hematopoietic precursor cell
Immune tolerance
Immunosuppressants
Infection
Ionizing radiation
Leukocyte
Lymphocyte
Mammal (Mammalia)
Rodent
Swine
T cell (lymphocyte)
Transplant and Transplantation
(method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Antibodies
Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT **Transplant and Transplantation**
(skin; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT **Hematopoietic precursor cell**

(stem; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Lymphatic system
(total **irradn.**; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Blood cell
Bone marrow
Heart
Skin
(transplant; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT Animal cell
(xeno- and allo-; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT **Transplant and Transplantation**
(xenotransplant; method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

IT 50-18-0, Cyclophosphamide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for inducing tolerance comprises administration of donor antigen and lymphocytotoxic agent to eliminate donor antigen-responding host T lymphocytes and transplantation of donor **hematopoietic** stem cells)

L71 ANSWER 11 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:744862 HCAPLUS
DN 130:33010
TI **Hematopoietic** cells, **hematopoietic** precursor cells, and/or matured lymphocytes contg. **tolerogen** as immunological tolerance-inducing agents
IN **Sugiura, Kikuya; Morita, Haruo; Ikehara, Susumu; Sogo, Shinji; Yamanishi, Kazuya;** Adachi, Shoichi
PA **Otsuka Pharmaceutical Co., Ltd., Japan**
SO Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K035-14
ICS A61K039-00; A61K038-00
CC 1-7 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 10306027	A2	19981117	JP 1997-155015	19970612 <--
PRAI JP 1997-52930		19970307 <--		

AB **Hematopoietic** cells, **hematopoietic** precursor cells, and/or matured lymphocytes contg. **tolerogens** given directly from portal vein followed by i.v. injections are claimed as immunol. tolerance inducing agents and can be used in organ transplants. Skin graft survival in mice was increased by the immunol. tolerance-inducing agents which also increased the effect of immunosuppressants e.g. cyclosporin A or FK 506.
ST immunotolerance **hematopoietic** cell lymphocyte organ transplant

IT Drug interactions
Hematopoietic precursor cell
Immunity
Immunosuppressants
Lymphocyte
Transplant and Transplantation
(**hematopoietic** cells, **hematopoietic** precursor cells, and/or matured lymphocytes contg. **tolerogen** as immunol. tolerance-inducing agents)

IT **Transplant and Transplantation**
(skin; **hematopoietic** cells, **hematopoietic** precursor cells, and/or matured lymphocytes contg. **tolerogen** as immunol. tolerance-inducing agents)

IT Skin
(transplant; **hematopoietic** cells, **hematopoietic** precursor cells, and/or matured lymphocytes contg. **tolerogen** as immunol. tolerance-inducing agents)

IT 59865-13-3, Cyclosporin A 104987-11-3, FK 506
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hematopoietic** cells, **hematopoietic** precursor cells, and/or matured lymphocytes contg. **tolerogen** as immunol. tolerance-inducing agents)

L71 ANSWER 12 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:542992 HCAPLUS
DN 129:160642
TI Tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue
IN Thall, Aron
PA Biotransplant, Inc., USA
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-48
CC 15-10 (Immunochemistry)
Section cross-reference(s): 1, **8**
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9833528	A2	19980806	WO 1998-US2103	19980205 <--
	WO 9833528	A3	19990211		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9863191	A1	19980825	AU 1998-63191	19980205 <--
	EP 969872	A2	20000112	EP 1998-907366	19980205 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001518074	T2	20011009	JP 1998-533214	19980205 <--
PRAI	US 1997-795925	A	19970205 <--		
	WO 1998-US2103	W	19980205 <--		

AB The invention provides methods and compns. for promoting in a first species a state of tolerance against Gal.alpha.1,3Gal epitopes present on a xenograft from a second species, thereby preventing hyperacute rejection (HAR) of the xenograft. In a first aspect, the invention provides methods

and **tolerogenic** compns. for inducing anergy in B-cells specific for the Gal.alpha.1,3Gal epitope. In a second aspect, the invention provides methods and **tolerogenic** compns. for inducing apoptosis in B-cells. In a third aspect, the invention provides methods and compns. for the cytotoxic elimination of memory B-cells and T-cells.

ST B cell tolerance xenograft epitope

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(M, membrane-assocd. (mIgM); elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue in conjunction with antibodies to)

IT Immunoglobulins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(M, xenoreactive; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Immunostimulants
(adjuvants, Freund's; in tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Immunostimulants
(adjuvants, Ribi; in tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT **Immune tolerance**
(anergy; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-IgM; elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue in conjunction with)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bcl-2, inhibitors; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Drug delivery systems
(carriers; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Erythrocyte
(cell membrane; in tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cholera, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Glycolipids
Saponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Cytotoxic agents
(conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Polymers, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg.

haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Ceramides
Glycoproteins, specific or class
Lipids, biological studies
Peptides, biological studies
Proteins, specific or class
Ricins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT CD38 (antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue in conjunction with antibodies to)

IT Immunoassay
Immunoassay
(enzyme-linked immunospot assay; for detection of B-cells producing natural anti-galactosyl antibodies)

IT Cell membrane
(erythrocyte; in tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Erythrocyte
(galactosyl-(.alpha.1.fwdarw.3)-galactose haptenic; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Trisaccharides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(galactosyl-(.alpha.1.fwdarw.3)-galactose-contg., conjugates; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Cerebrosides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexose-contg., conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hormones; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Drug delivery systems
(immunotoxins, anti-CD38; elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue with)

IT Alums
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Hemocyanins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(keyhole limpet, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipophilic, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Glycolipids
Phosphatidylcholines, biological studies
Phosphatidylethanolamines, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposomal; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Drug delivery systems
(liposomes; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT B cell (lymphocyte)
(memory; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Antibodies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(natural; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Glycoproteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoglycoproteins, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Antigens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-immunogenic cellular, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Lymphocyte
(plasma cell; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Polymers, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyglycomers, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum, conjugates, with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Hormones, animal, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(steroid; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT Apoptosis
B cell (lymphocyte)
(tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT T cell (lymphocyte)
(tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue and depletion of)

IT Swine

(tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue of)

IT Glycoconjugates
Radionuclides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT **Bone marrow**
Lymphocyte
(xenogeneic; in tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT **Transplant rejection**
(xenograft; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT **Transplant and Transplantation**
(xenotransplant; tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT 9003-05-8D, Polyacrylamide, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens 9004-54-0D, Dextran, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens, biological studies 68306-90-1D, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT 50-18-0, Cyclophosphamide 148-82-3, Melphalan 305-03-3, Chlorambucil 7440-26-8D, Technetium, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens, biological studies 9002-88-4 10043-66-0D, Iodine-131, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens, biological studies 10098-91-6D, Yttrium isotope of mass 90, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens, biological studies 23214-92-8D, Doxorubicin, conjugates with galactosyl-(.alpha.1.fwdarw.3)-galactose-contg. haptens 24280-93-1, Mycophenolic acid 25316-40-9, Adriamycin 35890-38-1D, HDPE conjugates 69655-05-6, 2',3'-Dideoxyinosine 75706-12-6, Leflunomide 96187-53-0D, Brequinar, analogs 119567-63-4, N,N-Dimethylsphingosine 128794-94-5 138686-73-4, N,N,N-Trimethylsphingosine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT 6705-50-6, 7-Oxanorbornene 211109-35-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(in prepn. of polyglycomers contg. galactosyl-(.alpha.1.fwdarw.3)-galactosyl hapten)

IT 141436-78-4, Protein kinase C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT 57-88-5, Cholesterol, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposomal; for tolerance and elimination of B-cells producing natural antibodies to galactosyl epitope expressed on xenograft tissue)

IT 13168-24-6DP, conjugates contg. 41744-59-6DP, conjugates contg. 77356-46-8DP, conjugates contg.
RL: ADV (Adverse effect, including toxicity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(tolerance and elimination of B-cells producing natural antibodies to)

L71 ANSWER 13 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1998:385255** HCAPLUS

DN **129:103920**
TI A new strategy for treatment of autoimmune disease in chimeric resistant MRL/lpr mice
AU Takeuchi, Kenji; Inaba, Muneo; Miyashima, Shigeo; Ogawa, Ryokei; **Ikehara, Susumu**
CS First Department of Pathology and Department of Orthopedic Surgery, Kansai Medical University, Osaka, 570, Japan
SO Blood (**1998**), 91(12), 4616-4623
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
CC 1-7 (Pharmacology)
Section cross-reference(s): **8**
AB A new strategy for the treatment of autoimmune diseases in chimeric resistant MRL/lpr mice is established. The strategy includes injection of cyclophosphamide (CY), fractionated **irradn.** (5 Gy .times. 2), bone grafts (to recruit stromal cells), and two transplantations of whole **bone marrow** cells (WBMCs) from allogeneic normal C57BL/6 mice (CY/2X/Bone/2BMT). MRL/lpr mice, thus treated, survived more than 40 wk (1 mouse survived for >40 wk, 7 for >50 wk, and 4 for >60 wk after these treatments). Immunohistol. studies showed that the mice were completely free from both lymphadenopathy and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. The levels of autoantibodies (IgM/IgG rheumatoid factors and IgM/IgG anti-ssDNA antibodies [Abs]) in the treated mice decreased to those in the normal mice. In addn., successful cooperation among T cells, B cells, and antigen-presenting cells (APCs) was obsd. Abnormal T cells with immunophenotypes of B220+/Thy-1+/CD3+/CD4-/CD8- present in untreated MRL/lpr mice disappeared, and the hematolymphoid cells of the treated mice were of donor origin. However, the mice that had been **irradiated** with 8.5 Gy and then reconstituted with T-cell-depleted BMCs plus bone grafts died within 2 wk due to the side effect of **irradn.** The depletion of CD8+ cells (not CD4+ cells) from WBMCs resulted in graft failure; 60% of the recipient mice, thus treated, died within 2 wk, and all recipients died by 15 wk. Furthermore, limiting diln. assays showed that approx. more than 0.5% of T cells contained in the BMCs are necessary not only for engraftment of BMCs but also for long-term disease-free survival of the recipients. In contrast, recipients that had received CD4-depleted BMCs with CY plus fractionated **irradn.** (5 Gy .times. 2) survived for more than 40 wk without showing graft-vs.-host reaction (GVHR). This indicates that CD8+ cells in the BMCs are essential for the successful engraftment of the donor-type hematolymphoid cells.
ST autoimmune disease cyclophosphamide **irradn** bone graft
IT Autoimmune disease
Immunosuppressants
Radiotherapy
(a new strategy for treatment of autoimmune disease in chimeric resistant MRL/lpr mice using cyclophosphamide and fractionated **irradn.** and bone graft and none marrow cell transplantations)
IT **Transplant and Transplantation**
(**bone marrow**; a new strategy for treatment of autoimmune disease in chimeric resistant MRL/lpr mice using cyclophosphamide and fractionated **irradn.** and bone graft and none marrow cell transplantations)
IT **Transplant and Transplantation**
(bone; a new strategy for treatment of autoimmune disease in chimeric resistant MRL/lpr mice using cyclophosphamide and fractionated **irradn.** and bone graft and none marrow cell transplantations)
IT Bone
Bone marrow
(transplant; a new strategy for treatment of autoimmune disease in chimeric resistant MRL/lpr mice using cyclophosphamide and fractionated

irradn. and bone graft and none marrow cell transplantations)
IT 50-18-0, Cyclophosphamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(a new strategy for treatment of autoimmune disease in chimeric resistant MRL/lpr mice using cyclophosphamide and fractionated **irradn.** and bone graft and none marrow cell transplantations)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L71 ANSWER 14 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:378509 HCAPLUS
DN 129:121303
TI A strategy for organ allografts without using immunosuppressants or **irradiation**
AU **Morita, Haruo**; **Sugiura, Kikuya**; Inaba, Muneo; **Jin, Tienan**; Ishikawa, Junji; Lian, Zhexiong; Adachi, Yasushi; **Sogo, Shinji**; **Yamanishi, Kazuya**; Taki, Hideo; **Adachi, Masakazu**; Noumi, Takato; Kamiyama, Yasuo; Good, Robert A.; **Ikehara, Susumu**
CS First Department of Surgery, Kansai Medical University, Moriguchi City, 570, Japan
SO Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(12), 6947-6952
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 15-1 (Immunochemistry)
AB A strategy to achieve regular and long lasting organ and tissue allografts without using immunosuppressants and/or **irradn.** has been established for mice. One hundred percent of skin allografts can be induced to survive >350 days after transplantation if spleen cells from

the same donors are first injected into the portal vein of the recipients. The mechanisms underlying this long-term tolerance induction can be described as follows: (i) donor T cells from the spleen of the donor facilitate the acceptance of the allogeneic engraftment, (ii) donor-specific anergy is induced in the cytotoxic T-lymphocytes of the recipients, (iii) T helper type 2 cells become the dominant T cells in the recipients that are accepting the skin transplants, and (i.v.) a lasting chimerism (microchimerism) is established in these recipients. This strategy, perhaps with minor modifications, might permit one also to overcome major barriers to organ allografting in humans. If this were the case, it could represent prodn. of long lasting immunol. tolerance without need for **irradn.** or cytotoxic chemo-preparative regimen and as such could greatly facilitate allotransplantation free of episodes of chronic or acute rejection or toxic and damaging preparatory regimens.

ST organ allograft tolerance strategy

IT **Transplant and Transplantation**
Transplant and Transplantation
(allotransplant, skin; strategy for organ allografts without using immunosuppressants or **irradn.**)

IT Skin
Skin
Transplant rejection
(allotransplant; strategy for organ allografts without using immunosuppressants or **irradn.**)

IT T cell (lymphocyte)
(cytotoxic; strategy for organ allografts without using immunosuppressants or **irradn.** in relation to)

IT **Immunosuppressants**
Radiation
(strategy for organ allografts without using immunosuppressants or **irradn.**)

IT **Immune tolerance**
T cell (lymphocyte)
(strategy for organ allografts without using immunosuppressants or **irradn.** in relation to)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L71 ANSWER 15 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1997:285412** HCAPLUS
DN **126:329380**
TI Acute graft versus host reaction (GVHR) against major / minor histocompatibility antigens
AU Takayanagi, Toshiaki; Kajino, Kiichi; Matsuki, Naoto; Iwabuchi, Kazuya; Ogasawara, Kazumasa; Onoe, Kazunori
CS Inst. Immunol. Sci., Hokkaido Univ., Sapporo, 060, Japan
SO Bone Marrow Transplantation: Basic and Clinical Studies, [Papers presented at the International Symposium on BMT--Basic and Clinical Studies], Tokyo, Oct. 9-10, 1995 (**1996**), Meeting Date 1995, 266-269. Editor(s): **Ikehara, Susumu; Takaku, Fumimaro; Good, Robert A.** Publisher: Springer, Tokyo, Japan.
CODEN: 64HVAW
DT Conference
LA English
CC 15-8 (Immunochemistry)
AB When **irradiated** minor lymphocyte stimulatory-1a (Mls-1a) mice were reconstituted with **bone marrow** cells plus mature T cells from Mls-1b and H-2 class I incompatible mice, acute GVHR was induced in the recipients. Majority of responding cells were shown to be CD4+V.beta.6+ T cells derived from donor mature T cells. It appeared that Mls-1a antigen (Ag) was a major target Ag. However, when Mls-1b donor and Mls-1a recipient mice were H-2 matched, the severity of GVHR was markedly reduced. Thus, disparity at the Mls-1 locus alone appeared not to be sufficient to induce detectable GVHR. In mixed lymphocyte reaction (MLR), T cell proliferation against Mls-1a plus H-2 class I Ag was as high as that against H-2 class I Ag alone. Prodn. of IL-2, IL-4 and TNF-.alpha. by the T cells responding to H-2 class I plus Mls-1a Ag was considerably greater than that by T cells responding to class I Ag alone. The present findings suggest that CD4+V.beta.6+ T cells responding to Mls-1a Ag and producing IL-2, IL-4 and TNF-.alpha. play a significant role, which may result in augmentation of allo-responses to the host H-2 class I Ag and substantial GVHR.
ST GVHR histocompatibility antigen T cell; H2 antigen mouse T lymphocyte GVHR
IT Histocompatibility antigens
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(H-2, class I; acute graft-vs.-host reaction in histocompatibility disparity)
IT Antigens
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(Mls (minor lymphocyte-stimulating), 1; acute graft-vs.-host reaction in histocompatibility disparity)
IT Cell proliferation
(T cell; acute graft-vs.-host reaction in histocompatibility disparity)
IT CD4-positive T cell
Mouse
(acute graft-vs.-host reaction in histocompatibility disparity)
IT Interleukin 2
Interleukin 4
Tumor necrosis factors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);

BIOL (Biological study); OCCU (Occurrence)
(formation by T-cells in relation to histocompatibility disparity and acute graft-vs.-host reaction)
IT **Transplant and Transplantation**
(graft-vs.-host reaction; acute graft-vs.-host reaction in histocompatibility disparity)
IT T cell (lymphocyte)
(proliferation; acute graft-vs.-host reaction in histocompatibility disparity)

L71 ANSWER 16 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1997:285394** HCAPLUS
DN **126:325953**
TI Effects of recombinant human thrombopoietin (rhTPO) on thrombopoiesis in **bone marrow**-transplanted mice
AU Kabaya, Koji; Shibuya, Kazunori; Torii, Yoshifumi; Akahori, Hiromichi; Nitta, Yuko; Ida, Masumi; Kato, Takashi; Miyazaki, Hiroshi
CS Japan
SO Bone Marrow Transplantation: Basic and Clinical Studies, [Papers presented at the International Symposium on BMT--Basic and Clinical Studies], Tokyo, Oct. 9-10, 1995 (**1996**), Meeting Date 1995, 94-100. Editor(s): **Ikehara, Susumu; Takaku, Fumimaro; Good, Robert A.** Publisher: Springer, Tokyo, Japan.
CODEN: 64HVAW
DT Conference
LA English
CC 2-10 (Mammalian Hormones)
AB We examd. whether recombinant human thrombopoietin (rhTPO) is capable of preventing thrombocytopenia and promoting thrombopoietic reconstitution following **bone marrow** transplantation (BMT) in mice. Immediately after receiving 10Gy whole-body **irradn.**, 7-wk-old male C3H/HeN mice were inoculated with 106 **bone marrow** cells obtained from syngeneic mice (day 0). In control mice undergoing BMT, platelet counts decreased below 5% of the normal counts with a nadir on day 10, and then returned to the normal level on day 28. Consecutive treatment with rhTPO at daily doses of 3 to 300.mu.g/kg s.c. from day 1 significantly prevented thrombocytopenia on day 10, and promoted the recovery on day 14 in a dose-dependent manner. A plateau was achieved by consecutive s.c. injections of 30.mu.g/kg. Variations in white blood cell counts and Hb concn. following BMT were not influenced by the rhTPO-treatment. We, then, investigated the administration schedule of rhTPO in this model. The rhTPO-injection starting from day 5 did not prevent thrombocytopenia on days 10 and 12 after BMT, but enhanced the recovery on day 14. Furthermore, administration with rhTPO on alternate days at 55.7.mu.g/kg/day for 7 days or at an interval of two days at 78.mu.g/kg/day for 4 days was less effective than consecutive administration at 30.mu.g/kg/day for 13 days. These findings suggest the usefulness of consecutive treatment with rhTPO from day 1 after BMT.
ST thrombopoietin thrombopoiesis **bone marrow** transplant
IT **Transplant and Transplantation**
(**bone marrow**; recombinant human thrombopoietin effects on thrombopoiesis in **bone marrow** transplant)
IT Platelet (blood)
(thrombocytopenia; recombinant human thrombopoietin effects on thrombopoiesis in **bone marrow** transplant)
IT Hematopoiesis
(thrombocytopoiesis; recombinant human thrombopoietin effects on thrombopoiesis in **bone marrow** transplant)
IT **Bone marrow**
(transplant; recombinant human thrombopoietin effects on thrombopoiesis in **bone marrow** transplant)
IT 9014-42-0, Thrombopoietin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(recombinant human thrombopoietin effects on thrombopoiesis in **bone marrow** transplant)

L71 ANSWER 17 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1996:433371 HCAPLUS
DN 125:84616
TI MHC class II tolerant T cells undergo apoptosis upon re-exposure to **tolerogen** in vivo
AU Alard, P.; Levy, R.; Kosiewicz, M.; Jones, M.; Streilein, J. W.
CS Schepens Eye Research Institute, Harvard Medical School, Boston, MA, 02114, USA
SO Transplant Immunology (**1996**), 4(1), 76-80
CODEN: TRIME2; ISSN: 0966-3274
PB Arnold
DT Journal
LA English
CC 15-10 (Immunochemistry)
AB Tolerance of MHC class II alloantigens can be achieved by i.v. injection of semiallogeneic **hematopoietic** cells into neonatal mice. Lymphoid cells of tolerant mice fail to proliferate or secrete interleukins IL-2 or IL-4 when stimulated in vitro with **tolerogen** . Since the lymphoid organs of B10.T(6R) tolerant mice contain normal levels of I-E reactive (V.beta.11+) CD4+ T cells, deletion of alloreactive T cells does not appear to be the mechanism involved in the tolerance induction. To test whether T cells from tolerant animals can become activated under conditions that do not involve alloantigen stimulation, the authors stimulated these cells with immobilized anti-V.beta.11 antibodies. Spleen cells from grafted tolerant and rejector mice proliferated in response to anti-V.beta.11+ antibodies, suggesting they were not inert. The authors then tested whether V.beta.11+ T cells from grafted mice can be induced to proliferate following stimulation with alloantigen in vivo. The authors adoptively transferred T cells from grafted tolerant and rejector mice into **irradiated** [B10.AQR .times. B10.T(6R)]F1 mice and harvested the lymphoid organs after 65 h. Cells from both grafted tolerant and rejector mice underwent blast transformation, but only cells from rejector mice proliferated when exposed to immobilized anti-V.beta.11 antibodies. The failure of V.beta.11+ cells from tolerant mice to proliferate after in vivo stimulation may be because they are apoptotic. To test this hypothesis, spleen cells from naive or neonatally tolerized with [B10.AQR .times. B10.T(6R)]F1 cells B10.T(6R) mice were adoptively transferred into **irradiated** [B10.AQR .times. B10.T(6R)]F1 mice and bcl-2 expression was analyzed in harvested V.beta.11+ cells. Large cells recovered from recipients of naive 6R cells expressed bcl-2 mRNA. By contrast, large cells harvested from recipients of tolerized 6R cells did not express bcl-2 mRNA, suggesting bcl-2 mRNA expression was downregulated in these mice. Moreover, in another expt., large V.beta.11+ cells from grafted tolerant animals recovered after transfer into **irradiated** [B10.AQR .times. B10.T(6R)]F1 mice did not express the bcl-2 protein as detd. by flow cytometry, and contained fragmented DNA as assessed by the TUNEL method. Thus, MHC class II tolerant T cells undergo apoptosis upon re-exposure to **tolerogen** in vivo.
ST MHC class II tolerance T lymphocyte; apoptosis T cell **tolerogen** MHC alloantigen
IT Apoptosis
Immune tolerance
Newborn
Transplant and Transplantation
(MHC class II tolerant T cells undergo apoptosis upon re-exposure to **tolerogen** in newborn tolerance model)

IT Histocompatibility antigens
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(MHC (major histocompatibility antigen complex), class II, MHC class II tolerant T cells undergo apoptosis upon re-exposure to **tolerogen** in newborn tolerance model)
IT Lymphocyte
(T-cell, MHC class II tolerant T cells undergo apoptosis upon re-exposure to **tolerogen** in newborn tolerance model)

L71 ANSWER 18 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1996:5461** HCAPLUS
DN **124:53539**
TI Prevention of Ipr-graft-versus-host disease and transfer of autoimmune diseases in normal C57BL/6 mice by transplantation of **bone marrow** cells plus bones (stromal cells) from MRL/Ipr mice
AU Miyashima, Shigeo; Nagata, Norikazu; Nakagawa, Takuma; Hosaka, Naoki; Takeuchi, Kenji; Ogawa, Ryokei; **Ikehara, Susumu**
CS First Department Pathology, Kansai Medical University, Osaka, Japan
SO Journal of Immunology (**1996**), 156(1), 79-84
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
CC 15-8 (Immunochemistry)
AB C57BL/6 (B6) (H-2b) mice were lethally **irradiated** and then reconstituted with T cell-depleted MRL/Mp-Ipr/Ipr (MRL/Ipr) (H-2k) **bone marrow** cells. The mice showed a short survival with splenic atrophy and fibrosis, as previously described as Ipr-graft-vs-host disease (GVHD). However, when these mice received **bone marrow** transplantation (BMT) plus bone grafts (to recruit donor-derived stromal cells) from MRL/Ipr mice, they survived for almost 1 yr without showing GVH symptoms, but showing autoimmune symptoms such as elevated serum IgG2a concns., autoantibody prodn. and glomerulonephritis. When MRL/Ipr **bone marrow** cells plus MRL/+ bones (instead of MRL/Ipr bones) were transplanted into B6 mice, such improved survival was also obtained, although the MRL/+ bone grafts were less effective in prolonging survival than MRL/Ipr bone grafts. H-2 typing of stromal cells in the **bone marrow** of the B6 mice revealed that the stromal cells had been replaced by donor (H-2k)-derived stromal cells. Analyses of TCR repertoires showed that the percentage of CD4+V.beta.8.1,2+ cells significantly decreased in the B6 mice that received **bone marrow** transplantation plus bone grafts from MRL/Ipr mice. These findings suggest that stromal cells present in the **bone marrow** play a crucial role in the development of Ipr-GVHD and autoimmune diseases.
ST Ipr graft versus host disease; autoimmune disease **bone marrow** transplant; stromal cell autoimmune disease GVHD
IT Autoimmune disease
(prevention of Ipr-graft-vs.-host disease and transfer of autoimmune diseases in normal C57BL/6 mice by transplantation of **bone marrow** cells plus bones (stromal cells) from MRL/Ipr mice)
IT **Transplant and Transplantation**
(graft-vs.-host reaction, Ipr-; prevention of Ipr-graft-vs.-host disease and transfer of autoimmune diseases in normal C57BL/6 mice by transplantation of **bone marrow** cells plus bones (stromal cells) from MRL/Ipr mice)
IT **Bone marrow**
(stroma, cells; prevention of Ipr-graft-vs.-host disease and transfer of autoimmune diseases in normal C57BL/6 mice by transplantation of **bone marrow** cells plus bones (stromal cells) from MRL/Ipr mice)
IT **Bone marrow**

(transplant, prevention of Ipr-graft-vs.-host disease and transfer of autoimmune diseases in normal C57BL/6 mice by transplantation of **bone marrow** cells plus bones (stromal cells) from MRL/Ipr mice)

L71 ANSWER 19 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1995:594898** HCAPLUS
DN **123:78629**
TI Cytotoxic effects of **irradiation** and deoxyguanosine on fetal thymus
AU Kumamoto, Takayuki; Inaba, Muneo; Toki, Junko; Adachi, Yasushi; Imamura, Hiroji; **Ikehara, Susumu**
CS Department of Thoracic Surgery, Kansai Medical University, Moriguchi, Japan
SO Immunobiology (**1995**), 192(5), 365-81
CODEN: IMMND4; ISSN: 0171-2985
DT Journal
LA English
CC 8-9 (**Radiation** Biochemistry)
AB Effects of **irradn.** and deoxyguanosine on the fetal thymus were examd. both in vitro and in vivo. Fetal thymus glands (gestation day 15) of C57BL/6 mice that had been **irradiated** (0-25 Gy) or treated with various doses of deoxyguanosine (dGuo) were engrafted under the renal capsules of BALB/c nu/nu mice, and the differentiation of T cells was investigated in the engrafted thymus gland or spleen of these mice. After in vitro treatment of fetal thymus glands with 1.35 mM dGuo (which was previously reported to be an optimal dose), T cell precursors still remained in some cultures, whereas 1.80 mM dGuo was highly cytotoxic not only to T cell precursors but also to thymic epithelial cells. In contrast, 25 Gy **irradn.** totally eliminated the T cell precursors from the fetal thymus, though the capacity of epithelial cells to induce T cell differentiation was retained. Although the **irradiated** thymus had the capacity to induce T cell differentiation when assayed in an in vitro organ culture system, long-term observation of thymus engrafted into BALB/c nu/nu mice revealed that, if they had been **irradiated** (9.5 Gy or 25 Gy), the thymus became scarred by 12 wks after transplantation. Furthermore, the expression of cell interaction mols. such as ICAM-1 and MHC class II on the thymus stromal cells decreased after **irradn.** The interaction mols. decreased 3 wks after 25 Gy **irradn.** and 7 wks after 9.5 Gy **irradn.** The alteration in T cell subsets in the thymus (decreases in both double- and single-pos. cells and an increase in double-neg. cells) correlated with the decreases in the interaction mols. This indicates that **irradn.** (even 9.5 Gy) impairs the T cell-induction capacity of the thymus stromal cells, resulting in an alteration of the T cell subsets followed by a change in the T cell counts in the thymus. Therefore, the long-term effects of **irradn.** on the thymus should be considered in cases of fetal thymus grafts or total body **irradn.** before **bone marrow** transplantation, particularly in the newborn.
ST cytotoxicity **irradn** fetus thymus gland; deoxyguanosine **irradn** fetus thymus gland
IT Gamma ray
(cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus)
IT Newborn
Transplant and Transplantation
(cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus in relation to **bone marrow** transplants)
IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ICAM-1 (intercellular adhesion mol. 1), cytotoxic effects of

irradn. and deoxyguanosine on fetal thymus)
IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus)
IT Hematopoietic precursor cell
Lymphocyte
(T-cell, cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus)
IT Embryo
(fetus, cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus)
IT Thymus gland
(stroma, cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus)
IT **Bone marrow**
(transplant, cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus in relation to **bone marrow** transplants)
IT 961-07-9, Deoxyguanosine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cytotoxic effects of **irradn.** and deoxyguanosine on fetal thymus)

L71 ANSWER 20 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:577592 HCAPLUS
DN 121:177592
TI Cellular mechanisms that maintain neonatally-induced tolerance of class II alloantigens. Evidence that factor-mediated suppression silences cytotoxic T cell activity
AU Matriano, James A.; Socarras, Sandra; Streilein, J. Wayne
CS School of Medicine, University of Miami, Miami, FL, 33136, USA
SO Journal of Immunology (**1994**), 153(4), 1505-14
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
CC 15-10 (Immunochemistry)
AB Virtually all neonatal mice of the a strain background are rendered profoundly and permanently tolerant of test skin allografts if they receive an i.v. inoculation of semiallogeneic **hematopoietic** cells expressing class II disparate alloantigens. After neonatally injected mice reach immunol. maturity, their lymphoid organs have been found to contain 1) **tolerogen**-specific CD4+ T cells that proliferate and secrete IL-4 when stimulated in vitro with class II **tolerogens** and 2) **tolerogen**-specific D8+ T cells that fail to differentiate into cytotoxic effector cells. In this study, expts. are described that investigate the possibility that tolerance is maintained by regulatory T cells of the Th2-type. When A.TH T cells were stimulated in vitro with A.TL alloantigens in the presence of lymphoid cells from tolerant mice, **tolerogen**-specific cytotoxic T cell responses were absent or greatly diminished. When regulatory cells from tolerant mice were fractionated and tested, the cell type responsible for suppression proved to be CD4+ class II **tolerogen**-specific and gamma **irradn.** sensitive. Moreover, suppression of **tolerogen**-specific cytotoxic T cell generation was achieved when regulatory cells and naive responder cells were sepd. by a transwell barrier and supernatants harvested from cultures in which tolerant cells were stimulated specifically with class II **tolerogens** also inhibited cytotoxic T cell generation. Thus, suppression appears to be mediated by a sol. factor(s) produced by regulatory T cells. The authors conclude that tolerance of class II alloantigens is maintained, at least

in part, by regulatory cells of the Th2-type that secrete factors that suppress the generation of **tolerogen**-specific effector cells required for rejection of solid tissue allografts.

ST class II antigen immune tolerance lymphocyte

IT **Immune tolerance**
(neonatally-induced, to class II alloantigens, mechanisms of)

IT Histocompatibility antigens
RL: BIOL (Biological study)
(MHC (major histocompatibility antigen complex), class II, neonatally-induced immune tolerance to, mechanisms of)

IT Lymphocyte
(T-cell, cytotoxic, neonatally-induced immune tolerance, to class II alloantigens in relation to)

IT Lymphocyte
(T-cell, helper cell/inducer, Th2, neonatally-induced immune tolerance, to class II alloantigens in relation to)

L71 ANSWER 21 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1989:185588 HCAPLUS
DN 110:185588
TI The necessity of both allogeneic antigens and stem cells for cyclophosphamide-induced skin allograft tolerance in mice
AU Mayumi, Hisanori; Good, Robert A.
CS Fac. Med., Kyushu Univ., Fukuoka, Japan
SO Immunobiology (**1989**), 178(4-5), 287-304
CODEN: IMMND4; ISSN: 0171-2985
DT Journal
LA English
CC 1-7 (Pharmacology)
Section cross-reference(s): 15

AB In an H-2 identical murine combination of AKR/J (AKR, H-2k, Thy 1.1) and C3H/HeJ (C3H, H-2k, Thy 1.2), specific tolerance to C3H skin in AKR mice is induced only when both i.v. 1 .times. 108 viable C3H spleen cells and, 2 days later, i.p. 200 mg kg cyclophosphamide (CP)/kg is given. **Irradiated** C3H spleen cells were used as an antigen source and **bone marrow** cells depleted of Thy 1.2+ and Ia+ cells as a stem cell source. When a mixt. of 1 x 108 **irradiated** spleen cells and 3 x 107 **bone marrow** cells was used as **tolerogen** and 200 mg CP/kg was administered 2 days later, a profound and specific long-lasting tolerance was induced. This tolerant state was less profound than that induced with spleen cells plus CP. When the no. of **irradiated** spleen cells was fixed at 1 .times. 108, the tolerant state was dose-dependent on the no. of **bone marrow** cells. When the no. of **bone marrow** cells was fixed at 1 .times. 106, tolerance induction depended on the no. of **irradiated** spleen cells. Tolerance induced with **irradiated** spleen cells plus **bone marrow** cells and CP was **tolerogen**-specific. Tolerance was never induced when the **bone marrow** cells had been **irradiated** with 2000 R prior to injection. The tolerant state in its acute phase was predominantly based on a redn. of functionally reactive cells. The prolongation of skin allograft survival in tolerant mice could not be attributed directly to suppressor cells, nor was any evidence of a suppressive factor induction obsd. In the chronic phase the importance of the suppressive mechanisms was relatively increased. EPICS anal. of thymocytes using fluorescein-conjugated anti-Thy 1.1 and anti-Thy 1.2 antibodies showed a minimal degree of mixed chimerism in the tolerant mice. Both T and Ia+ cells had beneficial effects on the induction of tolerance. Thus, in the tolerance induced by spleen cells plus CP, histocompatibility antigens expressed on the surface of the spleen cells were essential to the antigen-stimulated cell destruction mechanism. Stem cells contained in the spleen cells also were crucial for maintaining the tolerance by establishing a minimal degree of mixed chimerism.

ST cyclophosphamide antigen stem cell allograft skin
IT **Immunosuppression**
(by cyclophosphamide plus alloantigens plus stem cells, in skin grafts)
IT **Bone marrow**
Spleen
(cells of, skin transplant survival from cyclophosphamide plus)
IT **Transplant and Transplantation, animal**
(of skin, survival of, cyclophosphamide plus allogenic antigens plus stem cells in)
IT Antigens
RL: BIOL (Biological study)
(allo-, skin transplant survival from cyclophosphamide plus stem cells plus)
IT Skin
(transplant, survival of, cyclophosphamide plus allogenic antigens plus stem cells in)
IT 50-18-0, Cyclophosphamide
RL: BIOL (Biological study)
(skin transport survival from alloantigens plus stem cells plus)

L71 ANSWER 22 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN **1981:418360** HCAPLUS
DN **95:18360**
TI Specific immunosuppressive effects of constant infusion of 2'-deoxycoformycin
AU Trotta, Paul P.; Tedde, Antonio; **Ikehara, Susumu**; Pahwa, Rajendra; Good, Robert A.; Balis, M. Earl
CS Lab. Cell Metab., Mem. Sloan-Kettering Cancer Cent., New York, NY, 10021, USA
SO Cancer Research (**1981**), 41(6), 2189-96
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
CC 1-5 (Pharmacodynamics)
AB The effect of continuous infusion into C57BL/6J mice of 2'-deoxycoformycin (DCF) [70865-77-9], tight-binding inhibitor of adenosine deaminase, on the biol. function of **bone marrow** stem cells and T- and B-lymphocytes was evaluated. Greater than 85% inhibition of adenosine deaminase in erythrocytes, thymus, and **bone marrow** was noted after DCF infusion at 0.4 mg/kg/day, while lesser extents of inhibition were characteristic of spleen and lymph nodes. The reconstitution of lethally **irradiated** C57BL/6J mice with **bone marrow** cells from DCF- and 0.9% NaCl infused mice of the same strain was compared. The 2 groups of animals were virtually identical with respect to the no. of spleen colony-forming units, the response of splenic lymphocytes to both B- and T-cell mitogens, hematol. anal. of peripheral blood elements, and survival time, thus strongly supporting a lack of effect of DCF infusion on the capacity of stem cells to differentiate. In **contradistinction**, DCF infusion was highly lymphocytotoxic as noted by the severe necrosis in both B- and T-cell regions in lymph nodes and spleen and by the dramatic wt. redn. in spleen and thymus. Histopathol. of other tissues including **bone marrow** was normal except for the occurrence of hepatitis. A striking decrease in blastogenesis induced by the mitogens concanavalin A, phytohemagglutinin, and Escherichia coli lipopolysaccharides was also obsd. after DCF infusion. Consistent with these data, in vitro incubation of **bone marrow** cells with DCF did not impair the no. of spleen colony-forming units produced in lethally **irradiated** mice. These data suggest a potential use for adenosine deaminase inhibitors in the prevention of graft-vs.-host disease in hematopoietic transplantation.
ST deoxycoformycin immunosuppression lymphocyte toxicity
IT **Immunosuppression**

(from deoxycoformycin)
IT Lymphocyte
(B-, deoxycoformycin toxicity to)
IT Lymphocyte
(T-, deoxycoformycin toxicity to)
IT 70865-77-9
RL: BIOL (Biological study)
(immunosuppressive effects of and toxicity of to lymphocytes)

L71 ANSWER 23 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1979:150155 HCAPLUS
DN 90:150155
TI Studies on the resistance to tolerance induction against human IgG in DDD mice. I. Organ differences of **tolerogen** susceptibility and cellular sites responsible for the resistance
AU Hosono, Masamichi; Fujiwara, Michio
CS Inst. Med. Sci., Univ. Tokyo, Tokyo, Japan
SO Cellular Immunology (**1979**), 42(2), 279-88
CODEN: CLIMB8; ISSN: 0008-8749
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB Cellular sites of the **tolerogen** resistance in strain DDD mice against human IgG (HGG) were examd. by reconstitution expts. in which cells of various lymphoid organs from tolerized mice were transferred into lethally **irradiated** syngeneic recipients with or without the supplement of an excess no. of untreated T or B cells. T cells but not B cells in the spleen and **bone marrow**-locating B cells were **tolerogen** resistant. Kinetic profiles of tolerance induction were compared among thymus, lymph node, and spleen T cells. Thymus cells fall into unresponsive state as early as 2 days after the **tolerogen** (tHGG) injection when only partial tolerance was obsd. in lymph node T cells. By 1 wk of **tolerogen** treatment, the tolerant state was completed in both thymus cells and lymph node T cells, while spleen T cells showed marked resistance. Tolerance induced in thymus cells and spleen T cells was of relatively short duration and responsiveness was completely recovered by 5 wk after the injection of tHGG. At this time lymph node T cells still showed hyporesponsiveness. The differences in tolerance inducibility were also shown among different lymphoid organs in **tolerogen** dose response. Lymph node T cells were very sensitive to tolerance induction, giving no response even by the injection of 0.01 mg of tHGG. Thymus cells were much less sensitive with the gradual loss of responsiveness by increasing the amt. of tHGG. In contrast, spleen T cells showed gradual resistance with increasing amt. of tHGG, indicating that some pos. response was evoked in spleen T cells by a relatively high dose of tHGG. **Tolerogen** resistance of spleen T cells may be due to their capability of showing pos. response against the **tolerogenic** material. Also, treatment with cyclophosphamide following the **tolerogen** injection diminished completely the responsiveness against the subsequent challenge immunization.
ST immune tolerance IgG organ
IT Lymph gland
Spleen
Thymus gland
(in immune tolerance induction resistance to IgG)
IT **Immune tolerance**
(resistance to induction of, lymphocytes and organs in)
IT Immunoglobulins
RL: BIOL (Biological study)
(G, immune tolerance to, lymphocytes and organs in resistance to)
IT Lymphocyte
(T-, in resistance to immune tolerance to IgG)

L71 ANSWER 24 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1978:187957 HCAPLUS
DN 88:187957
TI Irreversible immunological tolerance to thymus-independent antigens is restricted to the clone of B cells having both Ig and PBA receptors for the **tolerogen**
AU Fernandez, C.; Moller, G.
CS Wallenberg Lab., Karolinska Inst., Stockholm, Swed.
SO Scandinavian Journal of Immunology (**1978**), 7(2), 137-44
CODEN: SJIMAX; ISSN: 0300-9475
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB Mice were tolerized to the .alpha.1-6 epitope of native dextran. When the spleen cells were removed and activated by lipopolysaccharide (LPS) they did not synthesize antibodies against the **tolerogen**. However, when cells from tolerant mice were treated with dextranase or left untreated in culture for 24 h they were activated by LPS to the synthesis of antibodies against the **tolerogen**. When 24 h tolerized lymphocytes were treated with dextranase and transferred with immunogenic doses of dextran to **irradiated** mice they failed to produce antibodies against the **tolerogen**. In contrast, cells incubated with dextran for 2 h and thereafter dextranase treated were readily immunized by dextran in the same system. It is concluded that only the B cell clones having both Ig receptors and polyclonal B cell activator (PBA) receptors for the **tolerogen** become irreversibly tolerized, whereas B cells having Ig receptors for a different PBA are not tolerized, but remain in a resting state, even though their Ig receptors have bound the **tolerogen**.
ST immune tolerance lymphocyte B receptor; dextran tolerance lymphocyte B receptor
IT Receptors
RL: BIOL (Biological study)
(for **tolerogen**, of B lymphocytes, of Ig and polyclonal B cell activator type, in irreversible immune tolerance)
IT **Immune tolerance**
(to thymus-independent antigens, Ig and polyclonal B cell activator receptors for **tolerogen** in relation to)
IT Lymphocyte
(**bone marrow**, Ig and polyclonal B cell activator receptors for **tolerogen** on, irreversible immune tolerance in relation to)
IT 9004-54-0, biological studies
RL: BIOL (Biological study)
(immune tolerance to, **tolerogen** receptors of B lymphocytes of Ig and polyclonal B cell activator type in development of irreversible)

L71 ANSWER 25 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1978:134759 HCAPLUS
DN 88:134759
TI Tolerance induced by TNP-derivatized syngeneic erythrocytes: evidence for cooperation between hapten-specific T and hapten-specific B lymphocytes in the immune response
AU Moody, Charles E.; Innes, Judith B.; Siskind, Gregory W.; Weksler, Marc E.
CS Dep. Med., Cornell Univ. Med. Coll., New York, NY, USA
SO Journal of Immunology (**1978**), 120(3), 844-9
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB Tolerance to the dinitrophenyl (DNP) haptenic determinant was induced with a single i.v. injection of trinitrophenylated syngeneic red blood cells (TNP-RBC). The tolerant state lasted 1 mo and was stable on transfer to

irradiated thymectomized syngeneic recipients. Suppressor activity was found soon after injection of **tolerogen** but was lost before the termination of tolerance. The unresponsive state could be reversed by adding normal thymus cells to tolerant spleen cells but not by normal **bone marrow** cells. Lipopolysaccharide (LPS) when given with immunogen restored the normal immune response in tolerant mice. Thus, the injection of mouse TNP-RBC induced partial immune unresponsiveness which was characterized by the induction of T cell suppressor activity and by a hapten-specific helper T cell tolerance. Finally, these studies suggest a cooperative interaction between DNP-specific T lymphocytes and DNP-specific lymphocytes in the immune response to DNP-bovine .gamma.-globulin.

ST immune tolerance dinitrophenyl lymphocyte

IT **Immune tolerance**
(to dinitrophenyl group, lymphocyte B-T cell cooperation in)

IT 2,4-Dinitrophenyl group
(tolerance to, lymphocyte B-T cell cooperation in)

IT Lymphocyte
(B-T cell, cooperation in immune tolerance to dinitrophenyl group)

IT Lymphocyte
(thymus, cooperation of, with **bone marrow** lymphocytes in immune tolerance to dinitrophenyl group)

L71 ANSWER 26 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1978:35778 HCAPLUS
DN 88:35778
TI Effect of lipopolysaccharide on immunogenicity and **tolerogenicity** of HGG in C57BL/6J nude mice: evidence for a possible B cell deficiency
AU Parks, D. Elliot; Doyle, Michael V.; Weigle, William O.
CS Dep. Immunopathol., Scripps Clin. Res. Found., La Jolla, CA, USA
SO Journal of Immunology (**1977**), 119(6), 1923-32
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB The in vivo and in vitro responses of nude mice to bacterial lipopolysaccharide (LPS) were detd. The in vitro responsiveness to LPS of spleen cells from congenitally athymic nude C57BL/6J mice was equiv. to littermate cells when monitored by stimulation of mitogenesis or polyclonal activation. Addnl., although nude spleen cells were incapable of responding to in vitro challenge with the T-dependent antigen, sheep red blood cells (SRBC), the addn. of LPS to these cultures promoted specific antibody synthesis indicating classical responsiveness of nude B cells to LPS in vitro. The effects of LPS upon responsiveness to human .gamma.-globulin (HGG) in vivo were also investigated. Deaggregated HGG (**tolerogen**) induced immune tolerance in the splenic B cells of these mice. This was stable on transfer into primed, **irradiated** recipients and persisted in nude mice for 4 mo. The induction of this tolerant state established in the absence of detectable T cell activity could be inhibited by the injection of LPS 3 h after the **tolerogen** . Although LPS was capable of inhibiting the induction of tolerance in nude mice in vivo, it was incapable of promoting the generation of specific antibody-secreting, plaque-forming cells (PFC) to either HGG or SRBC when injected with these T-dependent antigens. Addnl., LPS itself was recognized as a T-independent antigen by these nude mice. Although the induction of tolerance in the B cells of nude mice demonstrated that T cells are not required for induction or maintenance of B cell tolerance, the inability of nude B lymphocytes given LPS to respond to T-dependent antigens indicated that the signal received by B cells from the LPS mol. which replaces the requirement for helper T cells may be distinct from other LPS signals.

ST antibody tolerance globulin lipopolysaccharide

IT Lipopolysaccharides

RL: BIOL (Biological study)
(antibodies and tolerance to globulin response to, **bone marrow** lymphocyte in relation to)
IT Antibodies
RL: FORM (Formation, nonpreparative)
(formation of, lipopolysaccharides effect on, **bone marrow** lymphocyte in relation to)
IT **Immune tolerance**
(to .gamma.-globulins, lipopolysaccharides effect on, **bone marrow** lymphocyte in relation to)
IT Lymphocyte
(**bone marrow**, deficiency of, lipopolysaccharide effect on antibody and tolerance to .gamma.-globulins in relation to)
IT Globulins
RL: BIOL (Biological study)
(.gamma.-, antibodies and tolerance to, lipopolysaccharides effect on, **bone marrow** lymphocyte in relation to)

L71 ANSWER 27 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1977:550037 HCAPLUS
DN 87:150037
TI Influence of molecular structure on the **tolerogenicity** of bacterial dextrans. IV. Epitope size recognition and genetic resistance to .alpha. (1 .fwdarw. 3) glucosyl tolerance induction by dextran B1355
AU Howard, J. G.; Moreno, C.; Hale, Christine; Vicari, G.
CS Dep. Exp. Immunobiol., Wellcome Res. Lab., Beckenham, UK
SO European Journal of Immunology (**1977**), 7(7), 431-6
CODEN: EJIMAF; ISSN: 0014-2980
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB A basis was sought for the exceptional resistance of BABL/c mice to .alpha.(1.fwdarw.3) tolerance, for dextran B1355 behaved like a typical polysaccharide antigen in the CBA strain. The induction time for .alpha.(1.fwdarw.3) tolerance in CBA was even shorter (<6 h) than that for .alpha.(1.fwdarw.6), and the unresponsive state was as stable on cell transfer as .alpha.(1.fwdarw.6) tolerance in either strain. Although BALB/c mice are "high respnders" for the .alpha.(1.fwdarw.3) epitope, the B cell clone did not show any superior capacity to regenerate. Indeed, the slow recovery of responsiveness to both epitopes in **bone marrow**-reconstituted, **irradiated** mice was notably prolonged in the case of BALB/c. Antibody formation inhibition by oligosaccharides of the nigerose series revealed that the .alpha.(1.fwdarw.3) response corresponded to at least a tetrasaccharide determinant in CBA but to only a trisaccharide in BALB/c. As B cells specific for isomaltotetraose have a higher tolerance dose threshold than those for isomaltohexaose it seems probable that genetic resistance of BALB/c to .alpha.(1.fwdarw.3) tolerance depends on recognition of a relatively small epitope which could involve instability of binding between polysaccharide and B cell receptors.
ST immune tolerance dextran determinant genetics
IT Genetics
(of immune tolerance to dextran)
IT **Immune tolerance**
(to dextran, epitope size and genetics of)
IT Oligosaccharides
RL: BIOL (Biological study)
(tetra-, antibody formation inhibition by, dextran immune tolerance determinant in relation to)
IT Oligosaccharides
RL: BIOL (Biological study)
(tri-, antibody formation inhibition by, dextran immune tolerance determinant in relation to)

IT 497-48-3 6175-02-6 35997-20-7
RL: BIOL (Biological study)
(antibody formation inhibition by, dextran immune tolerance determinant in relation to)
IT 9004-54-0, biological studies
RL: BIOL (Biological study)
(immune tolerance to, epitope size and genetics of)

L71 ANSWER 28 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1975:561983 HCAPLUS
DN 83:161983
TI Influence of molecular structure on the **tolerogenicity** of bacterial dextrans. I. The .alpha.1-6-linked epitope of Dextran B512
AU Howard, J. G.; Vicari, G.; Courtenay, Barbara M.
CS Dep. Exp. Immunobiol., Wellcome Res. Lab., Beckenham, UK
SO Immunology (**1975**), 29(4), 585-97
CODEN: IMMUAM; ISSN: 0019-2805
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB Optimal immunization of BALB/c mice with i.v. dextran from Leuconostoc mesenteroides B512 at 1-10 .mu.g was succeeded by partial B-cell tolerance which developed progressively to total suppression at 10 mg. The tolerance threshold dose of dextran B512 was reduced 1000-fold during immunosuppression with cyclophosphamide (150 mg/kg, i.p.). The specificity of the response, detd. by plaque-forming cell assays using O-stearoyldextran B512, was directed towards an .alpha.1-6 epitope. High-dose tolerance was not preceded by immunity and was stable on cell transfer to **irradiated** mice in which responsiveness was obsd. after 4-6 weeks. There was a direct relation between inhibitory and **tolerogenic** activities both with dextran B512 fractions of varying mol. wt. and with heterologous dextrans, with both the immunogenicity and **tolerogenicity** of dextran B512 disappearing at mol. wts. .ltoreq.2 .times. 104. The effect of mol. structure on the **tolerogenicity** of polysaccharides to B cells is discussed in relation to these data and those in 2 accompanying papers.
ST dextran Leuconostoc **tolerogenicity** lymphocyte; immunogenicity dextran mol structure
IT Antigens
RL: BIOL (Biological study)
(Leuconostoc mesenteroides dextrans, structure and **tolerogenicity** in relation to)
IT Lymphocyte
(**bone marrow**, dextran tolerance of, structure in relation to)
IT Leuconostoc mesenteroides
(dextrans of, immunogenicity and **tolerogenicity** of)
IT Molecular structure-biological activity relationship
(immunogenicity and **tolerogenicity**, of dextrans)
IT **Immune tolerance**
(to dextran, mol. structure in relation to)
IT 9004-54-0, biological studies
RL: BIOL (Biological study)
(of Leuconostoc mesenteroides, immunogenicity and **tolerogenicity** of, mol. structure in relation to)

L71 ANSWER 29 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1974:503132 HCAPLUS
DN 81:103132
TI Tolerance induction to a thymus-dependent antigen in vitro. Treatment of nonadherent cells with **tolerogen** biologically filtered in vitro
AU Geyer, James W.; Kong, Yi-Chi M.
CS Sch. Med., Wayne State Univ., Detroit, MI, USA

SO Cellular Immunology (**1974**), 13(3), 447-58
CODEN: CLIMB8; ISSN: 0008-8749
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB Highly **tolerogenic** bovine .gamma.-globulin (BGG), a thymus-dependent antigen, was prepd. by biol. filtration in vitro. It readily induced tolerance in vivo in BALB/c mice and also rendered their nonadherent lymph node cells tolerant after in vitro incubation. Biol. filtration in vitro was carried out by incubating 2.5 .times. 107 lymph node cells with 10 mg of nontolerogenic BGG in 10 ml of Eagle's medium contg. 2% normal mouse serum at 37.degree. for 6 hr. The BGG-contg. medium was clarified by centrifugation and used without further diln. For tolerance induction in vitro, lymph node cells were sepd. into adherent and nonadherent populations on Falcon plastic. These cells were incubated for 0-18 hr at 37.degree. with biol. filtered BGG (bBGG). After incubation, the cells were washed 3 times and (2-2.5) .times. 107 nonadherent or 4 .times. 106 adherent cells were injected i.v. with their untreated counterpart into lethally **irradiated** mice which had received 106 **bone marrow** cells. The recipients were then challenged with 300 .mu.g of aggregated BGG, and tolerance was assayed by elimination of labeled BGG, rosette formation, and passive hemagglutination. Spleen cells were similarly treated for comparison. Data showed that tolerance was not induced in vitro in adherent lymph node cells. However, in the nonadherent populations, those from the lymph node but not the spleen were rendered tolerant. The acquisition of tolerance in vitro was gradual. It was dependent upon the length of exposure to bBGG and required at least 6 hr.
ST immune tolerance thymus dependence; antigen thymus dependent tolerance
IT Lymphocyte
(in immune tolerance to bovine .gamma.-globulins)
IT Antigens
RL: BIOL (Biological study)
(thymus-dependent, bovine .gamma.-globulins, immune tolerance to, lymphocyte in)
IT **Immune tolerance**
(to globulins bovine .gamma.-, lymphocyte in)
IT Globulins
RL: BIOL (Biological study)
(.gamma.-, immune tolerance to bovine, lymphocyte in)

L71 ANSWER 30 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1973:464447 HCAPLUS
DN 79:64447
TI Cellular basis of cross-tolerance
AU Ruben, Thomas J.; Chiller, Jacques M.; Weigle, William O.
CS Dep. Exp. Pathol., Scripps Clin. Res. Found., La Jolla, CA, USA
SO Journal of Immunology (**1973**), 111(3), 805-10
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB Mice made unresponsive to human .gamma.-globulin demonstrate a marked cross-tolerance to porcine .gamma.-globulin and equine .gamma.-globulin but react normally to the more phylogenetically distinct chicken .gamma.-globulin. This cross-tolerance exists in spite of an antigenic cross-reactivity at the indirect plaque-forming cell level of only 1 to 3%. This cross-tolerance status can be transferred to thymectomized, **irradiated**, **bone marrow**-reconstituted recipients by **tolerogen**-treated thymus cells. It is suggested that antigen recognition by the thymus-derived cell manifests a wider range of cross-reactivity than that evidenced by the **bone marrow**-derived cell.

ST cross tolerance immunity
IT Antigens
RL: PROC (Process)
(recognition of, by thymus lymphocyte, in immune tolerance to equine and human and porcine .gamma.-globulins)
IT Lymphocyte
(thymus, in immune tolerance to equine and human and porcine .gamma.-globulins)
IT **Immune tolerance**
(to .gamma.-globulins, equine and porcine .gamma.-globulins cross tolerance in)
IT Globulins
RL: BIOL (Biological study)
(.gamma.-, immune tolerance to, equine and porcine .gamma.-globulins cross-tolerance in)

L71 ANSWER 31 OF 32 HCAPLUS COPYRIGHT 2003 ACS
AN 1973:416791 HCAPLUS
DN 79:16791
TI Immunogenicity, **tolerogenicity**, and mitogenicity of lipopolysaccharides
AU Moller, Goran; Sjoberg, Olof; Andersson, Jan
CS Div. Immunobiol., Karolinska Inst., Stockholm, Swed.
SO Journal of Infectious Diseases (**1973**), 128(Suppl.), S52-S56
CODEN: JIDIAQ; ISSN: 0022-1899
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB Lipopolysaccharide (LPS) is an immunogen that often induces synthesis of IgM only. LPS can induce high-dose immunol. tolerance. Tolerant animals have an increased no. of antigen-binding cells, even though the no. of antibody-producing cells is depressed. Tolerance to LPS is rapidly broken by incubation of lymphocytes in tissue culture for 24 hr or by adoptive transfer of tolerant cells to **irradiated** hosts. LPS is a mitogen capable of activating DNA synthesis in **bone-marrow** (B) cells but not in thymus (T) cells. LPS-activated B cells secrete IgM antibodies against a variety of antigens. LPS-activated B lymphocytes differentiate into cells that produce antibody at a high rate and that express their genetrically detd. antibody specificity. LPS can substitute for both T cells and macrophages in the induction of a primary immune response in vitro. LPS acts directly on B cells and at least one function of the helper is immunol. nonspecific.
ST lipopolysaccharide antibody M; immunoglobulin M lipopolysaccharide; lymphocyte lipopolysaccharide DNA
IT Globulins, immune
RL: BIOL (Biological study)
(M, to lipopolysaccharide)
IT Lipopolysaccharides
RL: BIOL (Biological study)
(bacterial, antibodies and immune tolerance and lymphocyte in response to)
IT Lymphocyte
(**bone marrow**, antibody and DNA formation by, lipopolysaccharides effect on)
IT Mitogens
(lipopolysaccharides, **bone marrow** lymphocyte in response to)
IT **Immune tolerance**
Antibodies
RL: BIOL (Biological study)
(to lipopolysaccharides)

L71 ANSWER 32 OF 32 HCAPLUS COPYRIGHT 2003 ACS

AN 1973:95971 HCAPLUS
DN 78:95971
TI Cellular aspects of tolerance. II. Unresponsiveness of B cells
AU Kaplan, A. M.; Cinader, B.
CS Inst. Immunol., Univ. Toronto, Toronto, ON, Can.
SO Cellular Immunology (**1973**), 6(3), 442-56
CODEN: CLIMB8; ISSN: 0008-8749
DT Journal
LA English
CC 15-13 (Immunochemistry)
AB The responsiveness of **bone marrow** cells from tolerant donors was examd. by reconstitution of lethally **irradiated** **tolerogen**-free recipients. In these animals stem cells from tolerant donors gave rise to immunol. competent antigen-sensitive B cells. The antibody produced by these cells could be detected by a sensitive plaque assay in liq. and by antigen elimination. The antibody was not demonstrable by an assay which only detected plaque-forming antibody which was highly avid or was formed in large quantity per cell. In lethally **irradiated** animals partially purified B cells from a tolerant animal could not cooperate with T cells from normal donors to reconstitute immunol. responsiveness to immunogenic doses of the tolerance-inducing antigen. Antigen-sensitive B cells in the **bone marrow** become unresponsive following administration of **tolerogenic** forms of antigen. Responsiveness of the reconstituted recipient animals was due to the differentiation of donor stem cells and subsequent antibody prodn. by their descendants.
ST tolerance B cell
IT Lymphocyte
(**bone marrow**, unresponsive of, in immunetolerance)
IT **Immune tolerance**
(unresponsive lymphocyte of **bone marrow** in)

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/BIX is also provided which comprises both /BI and /ABEX <<<

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PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d all abeq tech abex tot

L118 ANSWER 1 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **2001-289818** [30] WPIX
CR 1996-238700 [24]; 1997-309774 [28]; 1999-189582 [16]; 2001-529007 [49]

DNC **C2001-088688**
TI Conditioning a recipient for **bone marrow** transplantation or hematopoietic reconstitution comprises using sublethal dose of total body **irradiation** and administration of monoclonal antibodies directed to natural killer cells.
DC B03 B04 D16
IN ILDSTAD, S T
PA (UYPI-N) UNIV PITTSBURGH
CYC 1
PI US 6217867 B1 20010417 (200130)* 78p A61K039-395 <--
ADT US 6217867 B1 **CIP of US 1993-120256 19930913, Div ex US 1994-337785 19941114, CIP of US 1997-785070 19970117, Provisional US 1998-73764P 19980205, US 1998-177704 19981022**
FDT US 6217867 B1 CIP of US 5514364, Div ex US 5635156, CIP of US 5876692
PRAI **US 1998-73764P 19980205; US 1993-120256 19930913 ; US 1994-337785 19941114; US 1997-785070 19970117; US 1998-177704 19981022**
IC ICM **A61K039-395**
ICS A61K031-00
AB US 6217867 B UPAB: 20011012
NOVELTY - Conditioning a recipient for **bone marrow** transplantation comprises subjecting recipient to total body **irradiation** (TBI) of 850-950 cGy and administering monoclonal antibodies directed to natural killer (NK) cells followed by transplantation of T-cell depleted donor cell preparation containing hematopoietic stem cells not compatible with the recipient at the major histocompatibility complex to achieve stable engraftment of donor hematopoietic stem cells without developing lethal graft-versus-host disease.

ACTIVITY - Immunosuppressive; antianemic; antisickling.

Recipient B10 mice received 1 of 3 conditioning approaches prior to transplantation with 40 multiply 106 or 1.5 multiply 106 BALB/c **bone marrow** cells: 70 mg/kg intravenous (i.v.) anti-lymphocyte globulin (ALG) given 3 days prior to **bone marrow** transplantation (group 1); 5 Gy of total body **irradiation** (TBI) on the day of transplantation (group 2); or both ALG and TBI as administered in groups 1 and 2 (group 3). Recipients were peripheral blood leukocyte (PBL)-types for evidence of allogeneic engraftment 2 months after **bone marrow** transplantation. Allogeneic chimerism occurred in 85% of the recipients conditioned with ALG and TBI, while no evidence of alloengraftment was seen in animal receiving either ALG or TBI alone.

MECHANISM OF ACTION - None given.

USE - The method is useful for preparing a recipient for **bone marrow** transplantation, and for conditioning an individual for hematopoietic reconstitution by **bone marrow** transplantation in the treatment of hematologic malignancies or disorders, autoimmunity, infectious diseases, e.g. AIDS, enzyme deficiency states, anemias, thalassemias, sickle cell disease, and the enlargement of **bone marrow** cells to induce tolerance for solid organ, tissue and cellular transplantation.

ADVANTAGE - The new method provides a stable mixed multilineage allogeneic chimerism and long-term donor-specific tolerance compared with previous methods of conditioning.

Dwg.0/24
FS CPI
FA AB; DCN
MC CPI: B04-G06; B04-G21; B11-C09; B14-F03; B14-G01B; **B14-G02C**; B14-G02D; D05-H11A
TECH UPTX: 20010603
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The recipient is further treated with an alkylating agent before, during or after TBI. The

total dose of TBI is preferably 900 cGy. The recipient may further be treated with anti-lymphocyte serum. The donor cell is obtained from a human, from a non-human primate, or from a pig. The donor cell preparation further comprises hematopoietic facilitatory cells having a phenotype of CD8+, alpha-beta-cell receptor (TCR)-, or delta-gamma TCR-.

ABEX

ADMINISTRATION - TBI is preferably administered between 850-950 cGy, preferably 900 cGy.

L118 ANSWER 2 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **2000-465973** [40] WPIX
CR 1999-045268 [04]; 2003-110146 [10]
DNC **C2000-140368**
TI Composition of cells which are endogenous to a first mammal and unresponsive to antigens of a second mammal are used for non-syngeneic cell therapy.
DC B04 D16 P14
IN PRIGOZHINA, T; SLAVIN, S
PA (BAXT) BAXTER INT INC; (HADA-N) HADASIT MEDICAL RES SERVICES & DEV
CYC 24
PI WO 2000040701 A2 20000713 (200040)* EN 119p C12N005-08
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA IL JP MX
EP 1141246 A2 20011010 (200167) EN C12N005-08
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6428782 B1 20020806 (200254) A61K038-00
JP 2002534083 W 20021015 (200282) 112p C12N005-06
ADT WO 2000040701 A2 WO 1999-US30704 19991223; EP 1141246 A2 EP 1999-968946 19991223, WO 1999-US30704 19991223; US 6428782 B1 **CIP of US 1997-862550 19970523, US 1998-222011 19981231**; JP 2002534083 W WO 1999-US30704 19991223, JP 2000-592399 19991223
FDT EP 1141246 A2 Based on WO 200040701; JP 2002534083 W Based on WO 200040701
PRAI **US 1998-222011 19981231; US 1997-862550 19970523**
IC ICM A61K038-00; C12N005-06; C12N005-08
ICS A01K067-027; A61K035-12; **A61K035-28; A61K039-00**; A61P035-00; A61P037-02; **A61P037-06**
AB WO 200040701 A UPAB: 20030211
NOVELTY - A cell population of lymphocytes endogenous to a first individual mammal and depleted of responsiveness to antigens of a second individual mammal, non-syngeneic to the first mammal, comprises 50-100% of a new composition (I) of cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of treating a host mammal with non-syngeneic cell therapy comprising infusing a cell population of lymphocytes previously depleted of responsiveness to antigens of the host mammal, from a donor mammal into the host mammal, where the donor and host mammal are non-syngeneic;

(2) a kit comprising packaging material and a biological cell container within the packaging material which has a composition containing hemopoietic stem cells for inducing non-syngeneic donor-specific tolerance in a host mammal by:

(a) administering donor antigens from a non-syngeneic donor to the host mammal;

(b) administering a non-myeloablative dose of lymphocytotoxic or tolerizing agent to the host mammal to selectively eliminate the host mammal's lymphocytes responding to the donor antigens; and

(c) administering a preparation of hematopoietic stem cells from the non-syngeneic donor to the host mammal;

(3) a kit comprising packaging material and a biological cell container within the packaging material which comprises (I); and

(4) a method of inducing tolerance in a host mammal to a graft from a non-syngeneic host mammal comprising:

(a) administering donor antigens from a non-syngeneic donor to the host mammal;

(b) administering an immunosuppressive agent to the host mammal in a non-myeloablative regimen to decrease the host mammal's functional T lymphocyte population;

(c) transplanting cells, a tissue or an organ from the donor into the host animal;

(d) administering a non-myeloablative dose of lymphocytotoxic or tolerizing agent to the host mammal to selectively eliminate the host mammal's lymphocytes responding to the donor antigens; and

(e) administering a preparation of hematopoietic stem cells from the non-syngeneic donor to the host mammal, where steps (a), (b) and (c) are performed on the same day and before steps (d) and (e).

ACTIVITY - Cytostatic; immunosuppressive; antianemic; antiarthritic; antirheumatic; dermatological; antiinflammatory; neuroprotective; antidiabetic; virucide; hepatotropic.

Donor lymphocytes pre-exposed to alloantigens of a patient were given to a female patient with Philadelphia chromosome positive (Ph+) CML. **Bone marrow** cells used in the transplantation were from a HLA-A, -B, -C and -DR identical 6 month old brother (the donor). The patients **bone marrow** contained 95% Ph+ cells prior to the allogenic cell therapy. Donor peripheral blood mononuclear cells (PBMC) (107 per kg) were administered intravenously (i.v.) 24 hours after a low dose of Cy (500 mg/m2). Then 107 per kg donor PBMC (activated in vitro with interleukin 2 (IL-2)) were administered i.v.. On the day of cell infusion rIL-2 (6 x 106 IU/m2/day) was administered subcutaneously for 3 days. The procedure was performed twice, one month apart, and resulted in transient decrease to 67% in proportion of Ph+ cells in the patients **bone marrow**. Paternal PBMC (6 x 106 activated in vitro with IL-2) were administered i.v. resulted in transient decrease to 60% in proportion of Ph+ cells in the patients **bone marrow**, followed by a gradual increase to 94% Ph+ **bone marrow** cells.

The patient was then treated with donor PBMC activated in vitro against alloantigens of the patient. Donor PBMC were activated to parental MHC antigens not expressed by the patient and MiHL antigens expressed by the patient but not the donor. The patient was then given rIL-2 (6 x 106 IU/m2/day) for three days starting on the day of infusion. The procedure was performed twice, one month apart, and interferon- alpha was administered 3 times a week for 4 years. The patient has now been in remission for more than 5 years, has no detectable leukemia cells and no clinical signs of GVHD (graft versus host disease).

MECHANISM OF ACTION - None given.

USE - The methods are for treating a host mammal to induce transplantation tolerance to cell, tissue and organ allografts and xenogafts and for improving the success of transplanting tissues and organs from a non-syngeneic donor to a host mammal. This can then be used for replacement therapy for enzyme or metabolic disorders, autoimmune diseases and adoptive immunotherapy for cancer and infections in humans.

Specifically the method is used to induce donor-specific tolerance in a host mammal to a graft from a non-syngeneic host (claimed).

The **tolerogenic** treatment provides a platform for subsequent allogeneic cell therapy for donor lymphocyte infusions in cancer patients and for other malignant and non-malignant diseases requiring **bone-marrow** transplantation.

(I) can be used to treat cancer patients, AIDS, hepatitis B or C, aplastic anemia, rheumatoid arthritis, multiple sclerosis, insulin-dependent diabetes mellitus, lupus erythematosus and myasthenia gravis.

Dwg.0/21

FS CPI GMPI

FA AB; DCN

MC CPI: B04-F04; B11-C09; B14-A02A5; B14-C03; B14-C09B; B14-F03; B14-G01B;

B14-G02C; B14-G02D; B14-H01; B14-N17; B14-S01; B14-S04; D05-H08

TECH UPTX: 20000823

TECHNOLOGY FOCUS - BIOLOGY - Preferred Composition: The lymphocytes are depleted of responsiveness through contacting the cells with antigens of the second individual mammal. The antigens comprise cancer cells. The first and second individual mammals are humans or the first individual mammal is a non-human primate and the second individual mammal is a human or the first individual mammal is a pig and the second individual mammal is a human.

Preferred Method: Depletion of responsiveness is carried out by contacting the cell population with a composition containing antigens expressed by the host mammal. The composition contains one or more antigen sources from cells, organs, tissues or non-cellular antigens, or the antigen is hemopoietic cells, or cancer cells, from the host mammal, expressing major histocompatibility complex molecules of the host mammal. A non-myeloablative dose of a lymphocytotoxic or tolerizing agent is then delivered to the lymphocyte population in vitro. Alternatively the antigens and the non-myeloablative dose are administered to the donor mammal. The population of lymphocytes is exposed, in vitro, to an immunosuppressive agent in a non-myeloablative regimen to decrease the number of functional T lymphocytes in the population. Alternatively the immunosuppressive agent is administered directly to the donor mammal. A preparation of hemopoietic stem cells is administered from the host mammal to the donor mammal.

Before infusion, tolerance to antigens of the donor mammal is induced in the host mammal by administering donor antigens to the host mammal, administering a non-myeloablative dose of lymphocytotoxic or tolerizing agent to the host mammal to selectively eliminate the host mammal's lymphocytes responding to the donor antigens and administering a preparation of hemopoietic stem cells from the non-syngeneic donor to the host mammal. Before this tolerance is induced an immunosuppressive agent may be administered to the host mammal in a non-myeloablative regimen to decrease the host mammal's functional T lymphocyte population. Depletion of responsiveness is achieved by substantially eliminating T cells from the population. Elimination is carried out by contacting the cells with mafosphamide, in vitro.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Agents: Immunosuppressive agents which are used include methotrexate, flurarabine, melphalan, thiotepa, busulfan, anti-lymphocyte globulin and ionizing **radiation**.

L118 ANSWER 3 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **2000-452301** [39] WPIX
DNC **C2000-137872**
TI Preventing or ameliorating transplantation rejection reactions using hydrolase enzymes.
DC B04 D16
IN FRANKLIN, R L; ST PIERRE, Y
PA (PHAI-N) PHAIRSON MEDICAL INC
CYC 86
PI WO 2000038708 A1 20000706 (200039)* EN 65p A61K038-43
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000028454 A 20000731 (200050) A61K038-43
ADT WO 2000038708 A1 WO 1999-US30818 19991223; AU 2000028454 A AU 2000-28454 19991223
FDT AU 2000028454 A Based on WO 200038708

PRAI **US 1998-114147P 19981224**
IC ICM A61K038-43
ICS A61K038-46; **A61K039-395**
AB WO 200038708 A UPAB: 20000818
NOVELTY - Preventing or ameliorating transplantation rejection reactions for transplantation of immune cells or other tissues comprises treating a source of immune cells with a hydrolase or hydrolase mixture and administering the treated immune cells to a recipient animal.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of identifying a hydrolase for use in preventing and or ameliorating allergic, autoimmune or transplantation reactions, comprising identifying and selecting one or more hydrolases with respect to a relative selective preference for removing, destroying, inactivating or disabling at least one of CD4, CD8, CD25, CD28, ICAM-1 (CD54), CD152, an integrin, CD154, CD40 and CD80 in contrast to removing, destroying, inactivating or disabling TcR; and

(2) a method of preventing or ameliorating transplantation rejection reactions comprising treating the donor tissue with a hydrolase or mixture of hydrolases which is more effective on a molar basis than the krill multifunctional enzyme.

ACTIVITY - Antiallergic; immunosuppressive; cytostatic.

Female mice (C57BL/6) were given a single dose of 700 r total body **irradiation** 2-4 hours before transplantation from a 60Co **irradiator**. **Irradiated** recipients were given a single intravenous injection via the tail vein of 5 x 106 **bone marrow** cells and 5 x 106 spleen cells as a source of T-cells. The spleen cells were treated with proteases (including purified krill-derived multifunctional enzyme (PHM)) before injection to **irradiated** recipients. Cleavage of CD4 and CD8 from the surface of T lymphocyte cell lines in vitro was dose-dependent. Ex vivo treatment of C57BL/6 splenocytes with PHM (50 micro g/ml for 2 hours at 37 deg. C) was sufficient to prevent the ability of splenocytes to induce lethal graft versus host disease (GVDH) in BDF1 recipients. BDF1 recipients receiving normal C57BL/6 splenocytes died within 4 weeks post-transfer.

MECHANISM OF ACTION - None given.

USE - The methods are useful for preventing graft versus host disease by using hydrolase enzymes to remove the cell surface adhesion molecules which are involved in triggering the immune reactions involved in the diseases. The methods are used for treating or preventing cell-cell or cell-virus adhesion syndrome comprising inflammation, shock, tumor metastases, autoimmune disease, transplantation rejection reactions or microbial injections.

Dwg.0/7
FS CPI
FA AB; DCN
MC CPI: B04-F02; B04-G02; B04-L05C; B14-G02A; **B14-G02C**; B14-G02D; B14-H01; D05-H
TECH UPTX: 20000818
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The treated immune cells are contacted with second cells from a donor animal and a tissue is transplanted from the donor animal to the recipient animal. The immune cells are treated with a cell surface-adhesion molecule antibody that binds to CD4, CD8, CD25, (IL-2 receptor alpha chain), CD28, CD125 (CTLA-4), an integrin, CD154, CD40 or CD80 is administered to the immune cells.

The source of immune cells is isolated from a donor fraction enriched in mature T cells and a fraction containing immune precursor cells, the mature T cells are treated with a hydrolase or mixture of hydrolases and the fractions are administered to a recipient. The hydrolase treated mature T cells are contacted with the immune precursor cells fraction before administration.

The immune cells are treated with a substance that induces the allergic

reaction or which contains autoimmune epitopes.
Preferred Hydrolases: The hydrolases induce tolerance in immune cells to a substance against which they were previously reactive or they have a relative selective preference for disabling signal 1 and/or signal 2. The hydrolase has a selective preference for removing, destroying, inactivating or disabling at least one of CD4, CD8, CD25, CD28, ICAM-1 (CD54), CD125, an integrin, CD154, CD40 and CD80 over removing, destroying, inactivating or disabling TcR. The selective preference is also for CD11a and CD49a over TcR (T cell receptor). The hydrolase is a protease, including a protease with a multifunctional activity comprising at least one of chymotrypsin, trypsin, collagenase, elastase or exo peptidase activity.

ABEX

ADMINISTRATION - Administration is systemic or applied to directly to affected tissues or cells. For organ transplants the organ, tissue or cells to be transplanted are bathed in a solution of the hydrolase (0.5 - 1250 U/ml) for between 10 minutes to 5 hours

L118 ANSWER 4 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **2000-109420** [10] WPIX
DNC **C2000-033357**
TI Pharmaceutical composition for haematopoietic stem cell transplantation - contains haematopoietic stem cells that are **irradiated** with an effective dose of **radiation** as active ingredient.
DC B04 B05
IN **IKEHARA, S**; INABA, M; KUSHIDA, T; TAKEUCHI, K
PA (**SAKA**) **OTSUKA PHARM CO LTD**; (NIMM) JAPAN IMMUNO RES LAB CO LTD
CYC 2
PI JP 11343242 A 19991214 (200010)* 18p A61K035-28 <--
US 6383481 B1 20020507 (200235) A61K035-28 <--
ADT JP 11343242 A JP 1999-58942 19990305; US 6383481 B1 US 1999-265418 19990310
PRAI JP 1998-84275 19980330
IC ICM **A61K035-28**
ICS A61K031-00; A61K035-14; C12N005-06
AB JP 11343242 A UPAB: 20000228
NOVELTY - Pharmaceutical composition contains haematopoietic stem cells as active ingredient. Haematopoietic stem cells are **irradiated** with an effective dose of **radiation** before transplantation.
USE - For treating autoimmune diseases (claimed), aplastic anemia, leukemia, malignant lymphoma, breast cancers and other cancers, blood stem cell disease and myelodysplastic syndrome (MDS). Cytostatic; antianemic; immuno-suppressive. Mice having lymphadenopathy were divided into two groups, one transplanted with **bone marrow** and to the other intraportal administration of twice **irradiated** with 5.5 Gy **radiation** of haematopoietic stem cell formulation was given. **Bone marrow** transplant recipients died within four weeks whereas 71% of haematopoietic stem cell recipient survived favorably for more than 40 weeks. None given.
ADVANTAGE - Rejection of transplanted cell due to graft Vs host reaction is eliminated and favorable maintenance of transplanted stem cells can be performed.
Dwg.0/0
FS CPI
FA AB
MC CPI: B04-F02; **B14-G02C**; B14-H01

L118 ANSWER 5 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1999-580364** [49] WPIX
DNC **C1999-168833**
TI Induction of T cell tolerance in sample of ex vivo peripheral blood mononuclear cells, useful for preventing Graft versus host disease.

DC B04
IN HORWITZ, D A
PA (UYSC-N) UNIV SOUTHERN CALIFORNIA
CYC 85
PI WO 9948524 A1 19990930 (199949)* EN 37p A61K039-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9930665 A 19991018 (200009)
EP 1061949 A1 20001227 (200102) EN A61K039-00 <--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6447765 B1 20020910 (200263) A61K045-00
US 2003012791 A1 20030116 (200308) A61K039-00 <--
ADT WO 9948524 A1 WO 1999-US4630 19990303; AU 9930665 A AU 1999-30665 19990303; EP 1061949 A1 EP 1999-912250 19990303, WO 1999-US4630 19990303; US 6447765 B1 **Provisional US 1998-76677P 19980303,** US 1999-261890 19990303; US 2003012791 A1 **Provisional US 1998-76677P 19980303,** Div ex US 1999-261890 19990303, US 2002-194344 20020711
FDT AU 9930665 A Based on WO 9948524; EP 1061949 A1 Based on WO 9948524; US 2003012791 A1 Div ex US 6447765
PRAI **US 1998-76677P 19980303;** US 1999-261890 19990303; US 2002-194344 20020711
IC ICM **A61K039-00;** A61K045-00
ICS A01N063-00; A01N065-00; A61K038-18; A61K038-19; A61K038-20; C12N005-08
AB WO 9948524 A UPAB: 19991124
NOVELTY - Inducing T cell tolerance in a sample of ex vivo peripheral blood mononuclear cells (PBMCs) comprises adding a suppressive composition to the cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(A) a method for treating donor cells to ameliorate graft versus host disease in a recipient patient comprising:

(i) removing peripheral blood mononuclear cells (PBMC) from a donor;

(ii) treating the cells with a suppressive composition for a time sufficient to induce T cell tolerance; and

(iii) introducing the cells to the patient; and

(B) a kit for the treatment of donor cells comprising:

(a) a cell treatment container adapted to receive cells from a donor; and

(b) at least one dose of a suppressive composition.

ACTIVITY - Immunosuppressive.

MECHANISM OF ACTION - The donor cells are activated to become tolerant to the recipient's cells, the donor CD8+ cells get activated to become regulatory cells to prevent other donor cells from killing recipient cells, therefore ameliorating a GVHD response.

USE - The method is useful for treating graft versus host disease (GVHD) in patients that have received allogenic **bone marrow** transplants e.g. acute or chronic leukemias, multiple myeloma, myelodysplastic syndromes, lymphomas and sever anemias e.g. aplastic anemia or thalassemia.

ADVANTAGE - The ex vivo protocol avoids the side effects experiences by administering in vivo cytokines and mitogens. It also avoids or minimizes the very toxic immunosuppressive medicines given to the recipient to prevent GVHD. They block the ability of the donor-derived lymphocytes which repopulate the immune response of the recipient from becoming educated to their new host. Therefore it is difficult to stop the immunosuppressive drugs. The donor lymphocytes become tolerant to the histocompatibility antigens of the recipient, but does not impair the ability of the new lymphocytes to attack tumor cells.

Dwg.0/4
FS CPI
FA AB; DCN
MC CPI: B04-F04; B04-H02L; B04-H06F; B11-C09; **B14-G02C**
TECH UPTX: 19991124
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The suppressive composition comprises a mixture of interleukin 10 (IL-10) and transforming growth factor beta (TGF-beta). The method further comprises adding the cells to donor stem cells prior to introduction into the patient. Preferred Kit: The kit further comprises written instructions for the treatment method. The dose is contained within the cell treatment container and is in lyophilized form. The cell treatment further comprises at least one reagent. The cell treatment container further comprises at least one reagent, a sampling port to enable the removal of a fraction of the cells for analysis and/or an exit port adapted to enable transport at least a portion of the cells to a recipient patient.
ABEX
EXAMPLE - A blood sample from a donor was obtained and lymphocytes prepared by density **gradient** centrifugation. T cells were prepared using a conventional negative selection procedure. The T cells were conditioned to prevent then from attacking the recipient cells. For this conditioning, the CD8+ T cells were mixed with **irradiated** stimulator cells from the recipient. The stimulator cells were derived from T cell-depleted blood cells from the recipient. The mixture of donor T cells and recipient stimulator cells were cultured 48 hours with different concentrations of one or more cytokines. The cytokines were transforming growth factor beta (TGF-beta) and interleukin 10 (IL-10), therefore abolishing the potential of the donor T cells to kill recipient cells.

L118 ANSWER 6 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1999-508455** [42] WPIX
CR 1999-479311 [40]
DNC **C1999-148469**
TI Promoting the acceptance of a xenograft within a receipient.
DC B04
IN SYKES, M
PA (GEHO) GEN HOSPITAL CORP
CYC 84
PI WO 9939726 A1 19990812 (199942)* EN 91p A61K038-16
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9925839 A 19990823 (200005) A61K038-16
EP 1053006 A1 20001122 (200061) EN A61K038-16
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002502823 W 20020129 (200211) 92p A61K045-00
AU 748443 B 20020606 (200249) A61K038-16
US 6514513 B1 20030204 (200313) A61F002-00
ADT WO 9939726 A1 WO 1999-US2443 19990204; AU 9925839 A AU 1999-25839 19990204; EP 1053006 A1 EP 1999-905749 19990204, WO 1999-US2443 19990204; JP 2002502823 W WO 1999-US2443 19990204, JP 2000-530223 19990204; AU 748443 B AU 1999-25839 19990204; US 6514513 B1 **Provisional US 1998-73864P 19980204**, US 1999-244447 19990204
FDT AU 9925839 A Based on WO 9939726; EP 1053006 A1 Based on WO 9939726; JP 2002502823 W Based on WO 9939726; AU 748443 B Previous Publ. AU 9925839, Based on WO 9939726
PRAI **US 1998-73864P 19980204**; US 1999-244447 19990204
IC ICM A61F002-00; A61K038-16; A61K045-00
ICS A61K038-00; A61K038-17; A61K038-18; **A61K039-395**;

A61P037-06; A61P043-00

AB WO 9939726 A UPAB: 20030224

NOVELTY - A method (A) of promoting acceptance, by a recipient mammal, of a graft from a donor mammal of a second species comprises:

(a) administering to the recipient, an inhibitor of a co-stimulatory pathway;

(b) introducing into the recipient mammal, hematopoietic stem cells; and

(c) implanting the graft in the recipient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method (B) of promoting acceptance, by a recipient mammal, of a graft from a donor mammal of the same species comprising:

(a) administering to the recipient, an inhibitor of a costimulatory pathway;

(b) introducing into the recipient mammal, hematopoietic stem cells; and preferably,

(c) implanting the graft in the recipient;

(2) a method (C) of promoting acceptance by a receipient mammal of a graft from a donor mammal comprising:

(a) administering to the recipient, an inhibitor of the co-stimulatory pathway;

(b) prior to or simultaneous with transplantation of the graft, introducing into the recipient mammal, donor thymic tissue; and

(c) implanting the graft in the recipient;

(3) a method (D) of promoting acceptance, by a recipient mammal of a graft from a donor mammal of the same species comprising:

(a) administering to the recipient, an inhibitor of a co-stimulatory pathway;

(b) introducing into the recipient mammal, hematopoietic stem cells, to achieve mixed hematopoietic chimerism without whole body **irradiation**; and

(c) implanting the graft in the recipient.

USE - The methods are useful for promoting the acceptance of a xenograft within a receipient.

ADVANTAGE - The methods can prevent chronic rejection in the recipient without damaging **radiation** therapy.

Dwg.0/10

FS CPI

FA AB; DCN

MC CPI: B04-F02; B04-F04; B04-G01; B04-G04; B11-C04A; B11-C09; **B14-G02**; **B14-G02C**

TECH UPTX: 19991014

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred materials: An inhibitor of the CD40 ligand-CD40 interaction and an inhibitor of the CD28-B7 interaction is administered. The CD40 ligand-CD40 interaction is inhibited by administering an antibody or soluble ligand or receptor for the CD40 ligand or CD40. An anti-CD40L antibody is administered. The CD28-B7 interaction is inhibited by administering a soluble ligand or receptor or antibody for the CD28 or B7. CTLA4/Ig is administered. CTLA4-Ig and an anti-CD40L antibody are administered. Alternatively, a blocker of the CD40/CD40L interaction is administered prior to administration of a blocker of the CD28/B7 interaction. The recipient mammal is a human and the donor mammal is a swine, especially a miniature swine. In (B), both the donor and the recipient are human.

Preferred methods: The methods are practiced without the administration of hematopoietic space-creating **irradiation**, without thymic **irradiation** or anti-T cell antibodies, without T cell depletion or inactivation, with partial T cell depletion or inactivation or with T cell depletion or inactivation. (A) includes hematopoictic space creating **irradiation**, at a dose of at most 100 cGy.

ABEX

EXAMPLE - Thymic **irradiation** (TI) or repeated administration of T cell-depleting mabs (TCD mabs) allows allogeneic marrow engraftment with

stable mixed chimerism and tolerance. Since both treatments might be associated with toxicity in the clinical setting, it was evaluated whether T cell costimulatory blockade could be used to replace them. C57BL/6 mice received depleting anti-CD4 and anti-CD8 mabs on day 5, 3 Gy whole body **irradiation** (WBI, day 0), and 15x106 fully MHC-mismatched, B10.A **bone marrow** cells (BMC). In addition, hosts were injected with an anti-CD154 mAb (day 0) and/or CTLA4Ig (day +2). Chimerism in peripheral blood was followed by FACS analysis, and tolerance was assessed by skin grafting, and also by MLR and CML assays. The frequency of certain VP families was determined by FACS to assess deletion of donor-reactive T cells.
Chimerism was transient and tolerance was not present in animals receiving TCDm Abs on day-5 without co-stimulatory blockade. The addition of anti-CD154 mAb (CD154 is also called CD40 ligand and gp39) and CTLA4Ig, alone or in combination, reliably permitted induction of high levels of stable (more than 6 months) multi-lineage chimerism, with specific tolerance to skin grafts and donor antigens by MLR and CML assays. Long-term chimeras showed deletion of donor-reactive CD4+ PBL, splenocytes and mature thymocytes. Administration of TCD mabs only one day prior to **bone marrow** transplantation (BMT) plus anti-CD154 mAb also allowed induction of permanent chimerism and tolerance. Thus, one injection of anti-CD154 mAb or CTLA4Ig overcomes the need for TI or prolonged host TCD for the induction of mixed chimerism and deletional tolerance and thus further decreases the toxicity of this protocol. Achievement of tolerance with conditioning given over 24 hours makes this approach even more useful for cadaveric organ transplantation.

L118 ANSWER 7 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1999-385126** [32] WPIX
DNC **C1999-113198**
TI Treatment of haematologic disorders.
DC B05
IN SPITZER, T R; SYKES, M
PA (GEHO) GEN HOSPITAL CORP
CYC 83
PI WO 9925367 A2 19990527 (199932)* EN 60p A61K035-14
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9915857 A 19990607 (199943) A61K035-14
EP 1030675 A2 20000830 (200042) EN A61K035-14
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 2001048921 A1 20011206 (200203) A61K039-395 <--
JP 2001523645 W 20011127 (200204) 75p A61K035-14
ADT WO 9925367 A2 **WO 1998-US24209 19981113**; AU 9915857 A **AU 1999-15857 19981113**; EP 1030675 A2 **EP 1998-960199 19981113, WO 1998-US24209 19981113**; US 2001048921 A1 **Provisional US 1997-73230P 19971114, US 1998-191970 19981113**; JP 2001523645 W **WO 1998-US24209 19981113, JP 2000-520800 19981113**
FDT AU 9915857 A Based on WO 9925367; EP 1030675 A2 Based on WO 9925367; JP 2001523645 W Based on WO 9925367
PRAI **US 1997-73230P 19971114; US 1998-191970 19981113**
IC ICM A61K035-14; **A61K039-395**
ICS A01N063-00; A01N065-00; A61K035-26; **A61K035-28**; A61P007-02; A61P035-02
ICI A61K031:675; **A61K035-28**, A61K039:395; **A61K035-28**; A61K039:395; A61K045:00; A61K031:675, **A61K035-28**, A61K039:395
AB WO 9925367 A UPAB: 20011203

NOVELTY - Treating haematologic disorders comprises administering a myeloreductive non-myeloblative or myeloreductive and immunosuppressive treatment to induce mixed hematopoietic chimerism and introducing allogeneic donor hematopoietic stem cells to form chimeric **bone marrow.**

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for treating neoplastic hematopoietic disorders which comprises administering a myeloreductive non-myeloablative treatment so that macroscopic mixed chimerism is induced in the subject and introducing allogeneic donor hematopoietic cells (mismatched at one or more HLA-A, B or DR antigens) to form chimeric **bone marrow** and induce a graft-versus-leukemia response and/or graft-versus-lymphoma response.

ACTIVITY - Anticancer.

MECHANISM OF ACTION - None given.

USE - The method is useful for treating neoplastic proliferation of hematopoietic cells, especially leukaemia and including lymphoblastic leukaemia, acute or chronic myelogenous leukaemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myelodysplastic syndrome, multiple myeloma and chronic lymphocytic leukaemia. The method is useful for treating haematologic disorders refractory to chemotherapy.

The method is also useful for treating non-malignant haematologic disorders including inherited erythrocyte abnormalities or inherited immune system disorders including sickle cell anaemia, aplastic anaemia and thalassemia.

ADVANTAGE - The methods reduce graft-versus-host disease, especially that associated with mismatched allogeneic or xenogeneic donor tissue.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: B04-G21; B05-B01J; B06-A02; B06-A03; B06-D09; B06-D18; B06-E03; B06-E04; B07-A02A; B07-A02B; B07-D09; B07-D12; B07-F01; B10-A07; B10-A09B; B10-A13D; B10-A17; B10-B01A; B10-B02A; B10-B04B; B14-F03; **B14-G02**; B14-H01A

TECH UPTX: 19990813

TECHNOLOGY FOCUS - BIOLOGY - The myeloreductive treatment includes treatment with an immunosuppressant regimen prior to introduction of the donor stem cells to prevent rejection of the donor stem cells. The method also comprises treatment with an immunosuppressant regimen after introduction of the donor stem cells to prevent a graft-versus-host response mediated by the donor cells and to prevent rejection of the donor stem cells.

The immunosuppressant regimen includes inactivating or depleting host T-lymphocytes and/or natural killer cells. The immunosuppressant regimen includes treatment with T-cell depleting anti-CD4and/or CD8 antibodies and/or treatment with anti-thymocyte globulin and/or treatment with OKT3, LO-CD2a, Minnesota anti-lymphoblast globulin and/or thymic **irradiation** and/or sub-lethal non-myeloablative **irradiation** of lymphocyte-containing tissue.

The myeloreductive treatment also includes treatment prior to introduction of the donor stem cells with a cytoreductive agent comprising an alkylating agent (e.g. nitrogen mustards, especially mechloretamine, cyclophosphamide, melphalan or chlorambucil), an alkyl sulphonate (e.g. busulphan), a nitrosourea (e.g. carmustine, lomustine, semustine or streptozocine), a triazine (e.g. dacarbazine), an antimetabolite (e.g. folic acid analogue such as methotrexate), a pyrimidine analogue (e.g. fluorouracil or cytarabine), a purine analogue (e.g. fludarabine, idarubicin, cytosine arabinoside, mercaptopurine or thioguanine), a vinca alkaloid (e.g. vinblastine, vincristine or vendesine), an epipodophyllotoxin (e.g. etoposide or teniposide), an antibiotic (e.g. dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin or mitomycin), dibromomannitol, deoxyspergualine, dimethyl myleran or thiotepa.

The donor stem cells are mismatched with respect to the subject at one or

more class II HLA antigens, preferably two or more HLA antigens and may be provided as allogeneic **bone marrow**, mobilised peripheral blood cells, cord blood cells or as ex vivo expanded stem cells.
The method also includes administration of allogeneic donor leukocytes after introduction of the donor stem cells, preferably at least 14 days after transplantation and if no GVHD is evident.

ABEX

EXAMPLE - Patients with chemotherapy and **radiation** refractory non-Hodgkin's lymphoma were treated with cyclophosphamide (50 mg/kg/day from day -6 to day -3), anti-thymocyte globulin (30mg/kg on days -2, -1 and +1), thymic **irradiation** (700cGy on day -1) and HLA genotypically identical (n = 2), phenotypically identical (n = 1) or 2 antigen mismatched donor **bone marrow** transplant (day 0). Cyclosporin was administered from day -1.
Donor leukocytes were given on day +35 (107/kg) and +56 (5x107/kg) if no graft-versus-host disease was present. HLA-matched marrow recipients all showed mixed chimerism. HLA-2 antigen mismatched recipients showed greater than 90% donor lymphoid chimerism within 2 weeks. All patients survived to a median of 103 days with 4/5 clinically disease free.

L118 ANSWER 8 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1998-495542** [42] WPIX
DNC **C1998-149236**
TI Immune tolerance inducer for patients undergoing organ transplant - comprises medicinal compositions for intra-portal and intravenous administration comprising **tolerogens** which contain haematopoietic cells, pre-haematopoietic cells and/or mature lymphocytes.
DC B04
IN **ADACHI, M; IKEHARA, S; JIN, T; MORITA, H; SOGO, S; SUGIURA, K; YAMANISHI, K**
PA (**SAKA**) **OTSUKA PHARM CO LTD**
CYC 20
PI WO 9839016 A1 19980911 (199842)* JA 37p A61K035-28 <--
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: US
JP 10306027 A 19981117 (199905) 7p A61K035-14 <--
JP 11180892 A 19990706 (199937) 4p A61K039-00 <--
EP 972519 A1 20000119 (200009) EN A61K035-28 <--
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9839016 A1 **WO 1998-JP909 19980304**; JP 10306027 A **JP 1997-155015 19970612**; JP 11180892 A **JP 1997-346737 19971216** ; EP 972519 A1 **EP 1998-905773 19980304, WO 1998-JP909 19980304**
FDT EP 972519 A1 Based on WO 9839016
PRAI **JP 1997-346737 19971216; JP 1997-52930 19970307** ; **JP 1997-155015 19970612**
IC ICM A61K035-14; **A61K035-28; A61K039-00**
ICS **A61N005-00**
ICA A61K038-00
AB WO 9839016 A UPAB: 19981021
An immune tolerance inducer for inducing immune tolerance in patients undergoing organ transplant comprises: (a) a first medicinal composition for intraportal administration which contains **tolerogens** containing haematopoietic cells, prehaematopoietic cells, mature lymphocytes or their mixtures as active ingredient; and (b) a second medicinal composition for intravenous administration which contains the above **tolerogens** and carrier. Also claimed are: (i) a drug for single administration to induce immune tolerance together with **radiation** comprising the above active ingredient and carrier; (ii) a method for inducing immune tolerance by administration of either of the above drugs; and (iii) production of the drugs using the **tolerogens**.

USE - The inducer is useful for sustaining transplanted organs without resorting to immunosuppressants and is especially useful in combination with **radiotherapy** (claimed).

ADVANTAGE - The method presents a procedure with little invasion.

Dwg.0/2

FS CPI
FA AB
MC CPI: B04-B04; B04-F02; **B14-G02C**

L118 ANSWER 9 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1998-041705** [04] WPIX
DNC **C1998-013857**
TI Promotion of transplant tolerance - by introducing haematopoietic stem cells from donor into recipient.
DC B04 B05
IN SYKES, M
PA (GEHO) GEN HOSPITAL CORP
CYC 76
PI WO 9741863 A1 19971113 (199804)* EN 53p A61K031-555 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU
AU 9731203 A 19971126 (199813) A61K031-555 <--
EP 918524 A1 19990602 (199926) EN A61K031-555
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6006752 A 19991228 (200007) A61B019-00
JP 2000511888 W 20000912 (200050) 64p A61K035-28 <--
EP 1048298 A2 20001102 (200056) EN A61K035-14
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 734665 B 20010621 (200141) A61K035-23
US 6412492 B1 20020702 (200248) A61B019-00
ADT WO 9741863 A1 **WO 1997-US7874 19970508**; AU 9731203 A **AU 1997-31203 19970508**; EP 918524 A1 **EP 1997-926433 19970508, WO 1997-US7874 19970508**; US 6006752 A **Provisional US 1996-17099P 19960509, US 1997-855705 19970508**; JP 2000511888 W **JP 1997-540229 19970508, WO 1997-US7874 19970508**; EP 1048298 A2 **Div ex EP 1997-926433 19970508, EP 2000-114769 19970508**; AU 734665 B **AU 1997-31203 19970508**; US 6412492 B1 **Provisional US 1996-17099P 19960509 , Div ex US 1997-855705 19970508**, US 1999-374498 19990813
FDT AU 9731203 A Based on WO 9741863; EP 918524 A1 Based on WO 9741863; JP 2000511888 W Based on WO 9741863; EP 1048298 A2 Div ex EP 918524; AU 734665 B Previous Publ. AU 9731203, Based on WO 9741863; US 6412492 B1 Div ex US 6006752
PRAI **US 1996-17099P 19960509; US 1997-855705 19970508** ; US 1999-374498 19990813
REP 5.Jnl.Ref; WO 9313785
IC ICM A61B019-00; A61K031-555; A61K035-14; A61K035-23; **A61K035-28**
ICS A61K031-47; A61K031-56; A61K035-12; A61K035-407; A61K038-00; A61K038-13; **A61K039-00**; **A61K039-395**; A61K041-00; **A61P037-06**
AB WO 9741863 A UPAB: 19980126
Promotion of transplant tolerance between the same or varying species comprises:(a) introducing into the recipient mammal, haematopoietic stem cells (HSCs) of the same or second species; (b) creating thymic space in the recipient, and (c) introducing the graft into the recipient, where the number of donor stem cells administered is sufficient such that mixed chimerism can be formed without haematopietic space-creating **irradiation.**

USE - The method can be used inducing transplant tolerance in e.g. liver and kidney (claimed) as well as heart, pancreas, bone and skeletal

matrix, skin, intestines, endocrine glands and progenitor stem cells of various types.

ADVANTAGE - The use of HSCs combined with the creation of thymic space can allow the induction of tolerance without the need for haematopoietic space-creating **irradiation**, especially whole body **irradiation** (claimed). The HSCs can promote engraftment, mixed chimerism and long-term deletional tolerance in graft recipients.

Dwg.0/5

FS CPI
FA AB
MC CPI: B04-F02; **B14-G02C**

L118 ANSWER 10 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1996-342058** [34] WPIX
CR 1998-333052 [29]
DNC **C1996-108617**
TI Reducing rejection of allo-graft(s) contg. antigen presenting cells - by treating transplant tissue with photosensitiser, then **irradiation** to destroy such cells, partic. for skin and pancreatic inlet grafts.
DC B02 B04 D16
IN LEVY, J; OBOCHI, M O K; OBOCHI, M
PA (QUAD-N) QUADRA LOGIC TECHNOLOGIES INC; (UYBR-N) UNIV BRITISH COLUMBIA
CYC 31

PI	WO 9621466	A1	19960718 (199634)*	EN 32p	A61K041-00	<--
	RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
	W: AU CA CN CZ FI HU JP KR MX NO NZ PL SK					
	AU 9643818	A	19960731 (199645)		A61K041-00	<--
	NO 9703251	A	19970908 (199747)		A61K000-00	<--
	EP 804238	A1	19971105 (199749)	EN	A61K041-00	<--
	R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
	FI 9702953	A	19970908 (199749)		A61K000-00	<--
	CZ 9702146	A3	19971217 (199807)		A61K041-00	<--
	SK 9700937	A3	19980114 (199812)		A61K041-00	<--
	AU 693634	B	19980702 (199837)		A61K041-00	<--
	HU 9801123	A2	19980828 (199844)		A61K041-00	<--
	MX 9705268	A1	19971001 (199901)		A61K041-00	<--
	KR 98701317	A	19980515 (199918)		A61K041-00	<--
	NZ 298355	A	20000228 (200017)		A61K041-00	
	TW 426518	A	20010321 (200151)		A61K035-12	
	JP 2001526623	W	20011218 (200203)	32p	A61K041-00	
	CN 1192157	A	19980902 (200276)		A61K041-00	<--

ADT WO 9621466 A1 **WO 1996-CA19 19960112**; AU 9643818 A **AU 1996-43818 19960112**; NO 9703251 A **WO 1996-CA19 19960112, NO 1997-3251 19970711**; EP 804238 A1 **EP 1996-900220 19960112, WO 1996-CA19 19960112**; FI 9702953 A **WO 1996-CA19 19960112, FI 1997-2953 19970711**; CZ 9702146 A3 **WO 1996-CA19 19960112, CZ 1997-2146 19960112**; SK 9700937 A3 **WO 1996-CA19 19960112, SK 1997-937 19960112**; AU 693634 B **AU 1996-43818 19960112**; HU 9801123 A2 **WO 1996-CA19 19960112, HU 1998-1123 19960112**; MX 9705268 A1 **MX 1997-5268 19970711**; KR 98701317 A **WO 1996-CA19 19960112, KR 1997-704706 19970710**; NZ 298355 A **NZ 1996-298355 19960112, WO 1996-CA19 19960112**; TW 426518 A **TW 1996-101405 19960205**; JP 2001526623 W **JP 1996-521344 19960112 , WO 1996-CA19 19960112**; CN 1192157 A **CN 1996-191452 19960112**

FDT AU 9643818 A Based on WO 9621466; EP 804238 A1 Based on WO 9621466; CZ 9702146 A3 Based on WO 9621466; AU 693634 B Previous Publ. AU 9643818, Based on WO 9621466; HU 9801123 A2 Based on WO 9621466; KR 98701317 A Based on WO 9621466; NZ 298355 A Based on WO 9621466; JP 2001526623 W Based on WO 9621466

PRAI **US 1995-371707 19950113**
REP 5.Jnl.Ref; US 5028594; US 5147289; WO 9503814

IC ICM A61K000-00; A61K035-12; A61K041-00
ICS A61K035-36; A61K035-39; **A61K039-00**; A61K045-00; **A61P037-06**
ICA C07D487-22
AB WO 9621466 A UPAB: 20021125
Redn. of the rejection of allografts comprising donor tissue contg. antigen-presenting cells (APC) is achieved by: (1) treating the tissue with a photosensitiser (I) and exposing to light at a wavelength absorbed by (I) to destroy APC, and (2) using the APC-depleted tissue as transplant. Also new are: (1) donor tissue treated this way and (2) compsn. of donor tissue contg. APC and conjugate that includes (I).
(I) are benzoporphyrin (BPD) derivs. and absorb at least partly in the visible spectrum. Partic. (I) is used as a conjugate with a targeting agent, esp. one that binds specifically to APC; suitable are antibodies (or their fragments) or receptor ligands. Alternatively, the targeting agent is a cpd. that binds to a label which in turn binds to APC. (I) is used as a 0.25-1 mu g/ml soln. and during **irradiation** the tissue is suspended in electrolyte soln., pref. of pH 6.5 and free of foetal bovine serum. Treatment is at about 10 J/cm2, at 15-37 deg. C. For skin grafts (1) may also be applied topically as a gel. Where grafts are to be stored, they are maintained in a perfluorochemical emulsion to ensure adequate oxygenation.
USE - The method is esp. applied to skin and pancreatic islets.
ADVANTAGE - Photodynamic destruction of APC significantly increases survival rate of the graft by preventing graft vs. host reaction, esp. for skin allografts. The treated tissue can be stored for 24-48 hrs., allowing establishment of graft banks. Donor tissue can be treated in vitro, avoiding the need to administer (I) to the host. The treatment does not kill keratinocytes but may alter expression of Class I/II molecules and secretion of cytokines so as to reduce the immunogenicity of the skin itself.
Dwg.3/1
FS CPI
FA AB; GI; DCN
MC CPI: B04-G21; B06-D18; B11-C09; **B14-G02C**; D05-H08; D05-H09

L118 ANSWER 11 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1994-100861** [12] WPIX
DNC **C1994-046452**
TI Inducing antigen specific immune tolerance - by deleting thymic dendritic cells then populating thymus with **tolerogenic** antigen presenting cells, for preventing graft rejection and treating auto-immune disease..
DC B04 D16
IN BESCHORNER, W E
PA (UYJO) UNIV JOHNS HOPKINS SCHOOL MED
CYC 1
PI WO 9405323 A1 19940317 (199412)* EN 44p A61K039-00 <--
W: CA
ADT WO 9405323 A1 **WO 1992-US7620 19920904**
PRAI **WO 1992-US7620 19920904**
REP 4.Jnl.Ref
IC ICM **A61K039-00**
ICS A01N063-00
AB WO 9405323 A UPAB: 19940510
Tolerance to an antigen (Ag) is induced by admin. to a recipient animal antigen, presenting cells (APC) enriched in cells **tolerogenic** for Ag, plus Ag. Also administered is at about the same time as APC; an immunosuppressant (I) to deplete the thymic medulla of dendritic cells.
Also new are methods for identifying A, (I) which cause depletion of the thymic medulla and (b) regeneration agents (II) able to restore a thymus depleted of medullary dendritic cells. Pref. the tolerance-inducing treatment is followed by admin. of (II).
USE/ADVANTAGE - The method is used to induce tolerance to allo-,

xeno- or auto-antigens. It is based on depletion of resident thymic APC, then repopulation of the thymus with **tolerogenic** cells.
Ag-specific tolerance is induced without the risks associated with long-term immunosuppressant therapy, and admin. of (II) accelerates thymic recovery.

In an example, rats were given total body **irradiation**, then 24 hrs. later they received 60 million mismatched **bone marrow** cells. Animals were given 15,g/kg/day (Ia) for 15 days then (a) no further treatment; (b) 30 million matched **bone marrow** cells or (c) as (b) but also 1.5mg/kg/day recombinant human (IIa) for 14 days. By day 97, 75% of animals given (a) had developed severe guest vs. host diseases but none of those in (b) or (c). The survival rates were 30% for (b) and 75% for (c).

Dwg.0/0

FS CPI
FA AB; DCN
MC CPI: B02-C01; B02-R; B04-F01; B04-J05; B04-J10; B10-A17; B12-K04A; **B14-G02**; B14-G02D; D05-H07; D05-H08; D05-H09; D05-H19

L118 ANSWER 12 OF 13 WPIX (C) 2003 THOMSON DERWENT
AN **1993-242903** [30] WPIX
CR 1993-182255 [22]; 1995-022263 [03]; 1995-022264 [03]; 1995-115396 [15]; 1995-194083 [25]; 1995-292892 [38]; 1995-336807 [43]; 1997-034106 [03]; 1997-424180 [39]; 1999-094387 [08]
DNN **N1993-186904** DNC **C1993-108216**
TI Method for inducing tolerance to xenografts - by absorbing natural antibodies by liver perfusion, administering anti-thymocyte globulin, **irradiation** of thymus, and **bone marrow** infusion.
DC B04 P34 S05
IN COSIMI, A; SACHS, D H; SYKES, M; COSIMI, A B
PA (GEHO) GEN HOSPITAL CORP
CYC 23
PI WO 9313785 A1 19930722 (199330)* A61K035-26 <--
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KP KR
AU 9334400 A 19930803 (199348) A61K035-26 <--
EP 621786 A1 19941102 (199442) EN A61K035-26 <--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 07503012 W 19950330 (199521) A61K039-395 <--
EP 621786 A4 19941214 (199543) A61K035-26 <--
AU 679437 B 19970703 (199735) A61K035-28 <--
AU 9739895 A 19980108 (199810) A61K035-28 <--
AU 2000030170 A 20000629 (200037)# A61K035-28 <--
US 6296846 B1 20011002 (200160) A61K048-00
EP 621786 B1 20020403 (200230) EN A61K035-26
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69331778 E 20020508 (200238) A61K035-26
ES 2172514 T3 20021001 (200275) A61K035-26
ADT WO 9313785 A1 **WO 1993-US184 19930107**; AU 9334400 A **AU 1993-34400 19930107, WO 1993-US184 19930107**; EP 621786 A1 **EP 1993-903046 19930107, WO 1993-US184 19930107**; JP 07503012 W **JP 1993-512596 19930107, WO 1993-US184 19930107**; EP 621786 A4 EP 1993-903046 ; AU 679437 B **AU 1993-34400 19930107**; AU 9739895 A **Div ex AU 1993-34400 19930107, AU 1997-39895 19971002**; AU 2000030170 A **Div ex AU 1997-39895 19971002**, AU 2000-30170 20000427; US 6296846 B1 **CIP of US 1992-817761 19920108, Cont of US 1992-838595 19920219, US 1995-451210 19950526**; EP 621786 B1 **EP 1993-903046 19930107, WO 1993-US184 19930107**; DE 69331778 E **DE 1993-631778 19930107, EP 1993-903046 19930107, WO 1993-US184 19930107**; ES 2172514 T3 **EP 1993-903046 19930107**

FDT AU 9334400 A Based on WO 9313785; EP 621786 A1 Based on WO 9313785; JP 07503012 W Based on WO 9313785; AU 679437 B Previous Publ. AU 9334400, Based on WO 9313785; EP 621786 B1 Based on WO 9313785; DE 69331778 E Based on EP 621786, Based on WO 9313785; ES 2172514 T3 Based on EP 621786

PRAI **US 1992-838595 19920219; US 1992-817761 19920108** ; AU 2000-30170 20000427; **US 1995-451210 19950526**

REP 8.Jnl.Ref; US 5087570; 2.Jnl.Ref; EP 341966

IC ICM A61K035-26; **A61K035-28; A61K039-395**; A61K048-00
ICS A61K035-12; A61K035-14; A61K035-407; A61K035-55; A61K043-00; A61K045-00; A61K051-00; **A61N005-00; A61N005-10; A61P037-06**

AB WO 9313785 A UPAB: 20021120
The use of haematopoietic stem cells from a mammal of a second species in the prepn. of a medicament to be introduced into a recipient mammal of a first, discordent species for inducing tolerance in the second species, where, prior to introducing the haematopoietic stem cells, an antibody capable of binding to natural killer cells of the recipient mammal is introduced into the recipient mammal.

Also claimed is (1) a method of preparing medicaments and devices for inducing tolerance in a recipient mammal to a graft obtd. from a donor mammal of the same species, comprising (a) admixing with a carrier haematopoietic stem cells obtd. a mammal so that the haematopoietic stem cells home to a site in the recipient mammal; (b) admixing with a carrier an antibody capable of binding to natural killer cells of the recipient mammal; (c) providing a perfusion device for haemoperfusing an organ obtd. from a mammal of the same species; and (d) providing a source of **radiation** for **irradiating** the recipient mammal with low dose **radiation** to partially deplete the **bone marrow** of the mammal.

ADVANTAGE - The antibody prevents natural killer cell-mediated rejection of the haematopoietic cells. The haematopoietic cells prepare the recipient for the graft by inducing tolerance at both the B-cell and T-cell levels.

Dwg.0/0

FS CPI EPI GMPI

FA AB

MC CPI: B04-B04A3; B04-B04C6; B12-D02A; **B12-D02B**
EPI: **S05-A03**

L118 ANSWER 13 OF 13 WPIX (C) 2003 THOMSON DERWENT

AN **1988-272832** [39] WPIX

DNC **C1988-121422**

TI Altering mammalian immune system - using altered mammalian system cells which have been stimulated by specific antigen.

DC B04 D16 P31 P34

IN EDELSON, R L; TRIPODI, D; TRIPODI, D J

PA (THER-N) THERAKOS INC

CYC 17

PI	EP 284409	A	19880928 (198839)* EN	16p		<--
	R: AT BE DE ES FR GB IT LU NL SE					
	AU 8813584	A	19880929 (198847)			<--
	DK 8801666	A	19880928 (198850)			<--
	JP 63275525	A	19881114 (198851)			<--
	PT 87086	A	19890330 (198916)			<--
	US 4838852	A	19890613 (198930)	9p		<--
	ZA 8802159	A	19891129 (199001)			<--
	CA 1306678	C	19920825 (199240)		A61K035-12	<--
	JP 2958372	B2	19991006 (199947)	13p	A61K039-00	<--

ADT EP 284409 A **EP 1988-302660 19880325**; JP 63275525 A **JP 1988-69892 19880325**; US 4838852 A **US 1987-31490 19870327**; ZA 8802159 A **ZA 1988-2159 19880325**; CA 1306678 C **CA 1988-562446 19880325**; JP 2958372 B2 **JP 1988-69892 19880325**

FDT JP 2958372 B2 Previous Publ. JP 63275525

PRAI **US 1987-31490 19870327**
REP 2.Jnl.Ref; A3...198906; EP 111418; EP 180452; EP 30358; No-SR.Pub; WO 8700053
IC ICM A61K035-12; **A61K039-00**
ICS A61B000-00; A61K035-14; A61K035-26; **A61K035-28**; **A61K039-39**; A61K041-00; A61M037-00; A61N000-00; C12N005-06; C12Q000-00; G01N000-00
AB EP 284409 A UPAB: 19991207
A method of producing a pharmaceutical compsn. comprising altered mammalian immune system cells comprises (a) withdrawing immune system cells form a mammal which has been artificially challenged with a specific antigen to stimulate the mammals immune system and (b) treating the withdrawn cells so as to alter cells stimulated by the antigen.

The immune system cells may be combined with a photoactivatable agent (I) and in step (b) the cells are **irradiated** with U.V. **radiation** so that (I) alters the cells. (I) may be a psoralen such as 8-methoxy psoralen or amino- methyl- trimethyl psoralen. The immune system cells may be withdrawn as blood, lymph fluid, **bone marrow** or lymphatic organ tissue and are pref. T. lymphocytes. The antigen may be one which is associated with a delayed hypersensitivity reaction, an autoimmune disease, a cancer, a allergy, an infectious disease, a rejection of allografts or a graft vs. host reaction.

USE/ADVANTAGE - The alteration of the immune system may result in either suppression or activation of the immune system, e.g., it may be suppressed so as to ameliorate the immune response to a specific antigen such as antigen associated with an allograft, or it may be activated in the case of a tumour antigen.
FS CPI GMPI
FA AB
MC CPI: B04-B04A3; B12-A01; B12-A06; **B12-D02B**; D05-H08
ABEQ US 4838852 A UPAB: 19930923
Changing the immune response of a patient to a specific antigen comprises injection of the specific antigen dispersion into the patient's bloodstream or immune system; removal of a blood sample contg. blood cells which have been stimulated by the antigen; activation of the sample by u.v. **irradiation** in the presence of a photoactivator, e.g. 8-methoxy-psoralene or aminomethyltrimethylpsoralene; and injection of the activated cells back into the patient's bloodstream or immune system.

USE - The process is applicable to the treatment of cancer, autoimmune diseases, allergies, infectious diseases and grafts.

=> fil medline
FILE 'MEDLINE' ENTERED AT 17:42:29 ON 17 MAR 2003

FILE LAST UPDATED: 16 MAR 2003 (20030316/UP). FILE COVERS 1958 TO DATE.

On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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L148 ANSWER 1 OF 7 MEDLINE
AN **2001401289** MEDLINE
DN **21348758** PubMed ID: **11455249**
TI A novel strategy for organ allografts using sublethal (7 Gy) irradiation followed by injection of donor bone marrow cells via portal vein.

AU Jin T; Toki J; Inaba M; Sugiura K; Fan T; Yu C; Lian Z; Takase K; Feng B; Ito T; Cui Y; Yang G; Ikehara S
CS First Department of Pathology, Kansai Medical University, 10-15 Fumizono-cho, Moriguchi City, Osaka 570-8506, Japan.
SO TRANSPLANTATION, (2001 Jun 27) 71 (12) 1725-31.
Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB A new strategy for organ allografts that does not require recourse to immunosuppressants is established in mice. The strategy includes sublethal (7 Gy) irradiation followed by the injection of donor bone marrow cells (BMCs) via the portal vein (P.V.) and organ allografts 1 day after irradiation. Irradiation doses (< or =7 Gy) are found to allow the recipients to survive without the need to reconstitute the BMCs, as the recipient hematolymphoid cells can gradually recover. One hundred percent of recipients irradiated with 7 Gy followed by either P.V. or i.v. injection of donor BMCs accept organ allografts (the skin, pancreas, and adrenal glands) for more than 1 year. However, organ allograft survival rates decrease when irradiation doses are reduced; the skin graft survival rate of mice treated with 6.5 Gy and P.V. injection of BMCs is 79%, whereas that of mice treated with 6.5 Gy and i.v. injection is 50%, indicating that the P.V. injection of BMCs induces persistent tolerance more effectively than the i.v. injection. H-2 typing reveals that almost all the hematolymphoid cells (>98%) in the peripheral blood and hematolymphoid organs are donor-derived even 1 year after the treatment (7 Gy and P.V.). The T cells are tolerant to both donor-type and host-type MHC determinants. The major mechanism underlying the persistent tolerance induced by this strategy seems to be because of clonal deletion. This simple and safe strategy would be of great advantage for human organ transplantation.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Adrenal Glands: TR, transplantation
***Bone Marrow Cells: TR, transplantation**
***Bone Marrow Transplantation: MT, methods**
Chimera
Graft Survival
Immune Tolerance
Injections, Intravenous
Mice
Mice, Inbred Strains
***Organ Transplantation**
Pancreas Transplantation
***Portal Vein**
*Preoperative Care
Skin Transplantation
Survival Analysis
Transplantation Immunology
Transplantation, Homologous
***Whole-Body Irradiation**

L148 ANSWER 2 OF 7 MEDLINE
AN **1998090382** MEDLINE
DN **98090382** PubMed ID: **9430517**
TI Enhanced engraftment of intravenously transplanted hematopoietic stem cells into bone marrow of irradiated mice treated with AcSDKP.
AU Suzuki A; Aizawa S; Araki S; Hoshi H; Nakano M; Kimura Y; Toyama K
CS First Department of Internal Medicine, Tokyo Medical College, Japan.

SO EXPERIMENTAL HEMATOLOGY, (1998 Jan) 26 (1) 79-83.
Journal code: 0402313. ISSN: 0301-472X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980204
AB The effect of the tetrapeptide Acetyl-N-Ser-Asp-Lys-Pro (AcSDKP) on intravenously transplanted hematopoietic stem cell engraftment into the bone marrow (BM) of irradiated mice was studied. When 5 x 10(4) marrow cells were transplanted into lethally irradiated mice given 10 microg AcSDKP, the survival of these animals 4 weeks posttransplantation increased markedly from 20.0 +/- 4.4% to 86.1 +/- 4.8%, the same result as that obtained from mice transplanted with 5 x 10(5) cells without AcSDKP treatment. Increased numbers of hematopoietic stem cells, including spleen colony-forming unit and colony-forming unit granulocyte-macrophage, were observed in the BM of AcSDKP-treated mice 1 and 8 days after transplantation. This finding suggested that AcSDKP influenced homing of hematopoietic stem cells into the BM of lethally irradiated animals. This enhancing activity of AcSDKP was neutralized by the simultaneous administration of an anti-AcSDKP polyclonal antibody. Furthermore, recovery of leukocytes in peripheral blood occurred faster in AcSDKP-treated than in untreated transplanted mice. These findings may provide a basis for the clinical use of AcSDKP in BM transplantation patients.
CT Check Tags: Animal; Male
*Graft Survival: DE, drug effects
***Hematopoietic Stem Cell Transplantation**
Injections, Intravenous
Mice
Mice, Inbred C3H
*Oligopeptides: AD, administration & dosage
*Radiation-Protective Agents: AD, administration & dosage
Transplantation, Homologous
Whole-Body Irradiation
RN 120081-14-3 (goralatide)
CN 0 (Oligopeptides); 0 (Radiation-Protective Agents)

L148 ANSWER 3 OF 7 MEDLINE
AN **94122155** MEDLINE
DN **94122155** PubMed ID: **8292574**
TI Implanted right atrial catheters for continuous infusion of solutions into dogs.
AU Dennis M B Jr; Graham T C; Raff R F; Jones D R; Schuening F; Storb R
CS Department of Comparative Medicine School of Medicine, University of Washington, Seattle 98195.
NC NCI CA31787 (NCI)
NCRR RR01203 (NCRR)
NIDDK DK42716 (NIDDK)
SO JOURNAL OF INVESTIGATIVE SURGERY, (1993 Sep-Oct) 6 (5) 461-7.
Journal code: 8809255. ISSN: 0894-1939.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940314
Last Updated on STN: 19940314
Entered Medline: 19940303
AB Silastic catheters were fabricated and aseptically implanted through the

skin into the jugular vein of 64 dogs with the intravascular tip located in the right atrium. Solutions were infused through the catheter at 2 to 2.5 mL/h by a portable pump worn by the dog. Following 9.2 Gy total body irradiation (TBI) and allogeneic bone marrow transplantation (BMT), succinyl acetone, an experimental chemotherapeutic agent, was infused into 34 dogs. Hematopoietic growth factors were infused into an additional 30 dogs, two of which had 9.2 Gy TBI and an autologous BMT, and four of which had 4.0 Gy TBI and no BMT. All dogs received continuous oral and parenteral antibiotics while the catheters were in place. All catheters functioned well until electively removed (n = 28) or until the dogs died or were euthanized (n = 36) at 12 to 68 days after implantation. Mean length of catheter function was 30.3 +/- 1.5 (SEM) days. No catheters were dislodged and there was no evidence of catheter-related blood loss or sepsis. Semiquantitative cultures of 5 catheters were negative, but Staphylococcus epidermidis was isolated from 3 of 7 catheters cultured in broth. Six dogs had thrombosis adjacent to the intravascular catheter tip. The catheters were well tolerated and facilitated successful long-term infusion of solutions into dogs.

CT Check Tags: Animal; Female; Male; Support, U.S. Gov't, P.H.S.
Bacterial Infections: ET, etiology
Bone Marrow Transplantation
***Catheters, Indwelling**
Dogs
Heart Atrium
***Heart Catheterization**
***Hematopoietic Cell Growth Factors: AD, administration & dosage**
*Immunosuppressive Agents: AD, administration & dosage
Infusions, Intravenous
Jugular Veins
Reproducibility of Results
Silicone Elastomers
Time Factors
Whole-Body Irradiation: AE, adverse effects

CN 0 (Hematopoietic Cell Growth Factors); 0 (Immunosuppressive Agents); 0 (Silicone Elastomers)

L148 ANSWER 4 OF 7 MEDLINE
AN **93114385** MEDLINE
DN **93114385** PubMed ID: **8417949**
TI Continuous intravenous administration of rmGM-CSF enhances immune as well as hematopoietic reconstitution following syngeneic bone marrow transplantation in mice.
AU Naparstek E; Ohana M; Greenberger J S; Slavin S
CS Department of Bone Marrow Transplantation, Hadassah University Hospital, Jerusalem, Israel.
NC CA39851 (NCI)
SO EXPERIMENTAL HEMATOLOGY, (1993 Jan) 21 (1) 131-7.
Journal code: 0402313. ISSN: 0301-472X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199301
ED Entered STN: 19930219
Last Updated on STN: 19930219
Entered Medline: 19930129
AB Lethally irradiated Balb/c mice injected with syngeneic bone marrow cells received recombinant murine granulocyte/macrophage colony-stimulating factor (rmGM-CSF) by continuous intravenous infusion for 4 days. When transplanted with 10(5) marrow cells, treated mice showed higher survival (62% compared with 30% in the control group, $p < 0.001$) and significantly enhanced hematopoietic recovery manifested by 11-fold increase in the peripheral white blood cell (WBC) count. Day 7 marrow from

rmGM-CSF-treated mice resulted in 70% survival in lethally irradiated secondary recipients, while marrow harvested under identical experimental conditions from saline-treated mice had no reconstituting capacity at all. When mice were injected with 10(4) marrow cells, 20% of rmGM-CSF treated mice survived as compared with none in the controls. In vitro preincubation of 10(5) and 5 x 10(5) fresh bone marrow cells with rmGM-CSF prior to transplant significantly improved survival of lethally irradiated mice in comparison with control (12% and 37.5% respectively, $p < 0.001$). Proliferative responses of lymphocytes obtained from rmGM-CSF-treated mice to mitogens and allogeneic C57BL6 splenocytes as well as non-MHC restricted cytotoxicity against tumor cells were significantly higher in rmGM-CSF-treated mice as compared with controls ($p < 0.01$). These data suggest that a short course of continuous intravenous infusion of rmGM-CSF following BMT or in vitro culturing of bone marrow cells with rmGM-CSF improves marrow reconstituting capacity. The mechanism may be by enhancing proliferation and function of committed and perhaps even the more primitive progenitor cell.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Bone Marrow Cells
***Bone Marrow Transplantation**
Concanavalin A: PD, pharmacology
***Granulocyte-Macrophage Colony-Stimulating Factor: AD, administration & dosage**
Granulocyte-Macrophage Colony-Stimulating Factor: PD, pharmacology
***Hematopoiesis**
*Immunity
Infusions, Intravenous
Killer Cells, Lymphokine-Activated: IM, immunology
Lipopolysaccharides: PD, pharmacology
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Phytohemagglutinins: PD, pharmacology
Recombinant Proteins: AD, administration & dosage
Spleen: CY, cytology
Spleen: IM, immunology
Whole-Body Irradiation

RN 11028-71-0 (Concanavalin A); 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)

CN 0 (Lipopolysaccharides); 0 (Phytohemagglutinins); 0 (Recombinant Proteins)

L148 ANSWER 5 OF 7 MEDLINE

AN 93054390 MEDLINE

DN 93054390 PubMed ID: 1429487

TI Collection of blood mononuclear cells by leukapheresis for transplantation in a Yucatan miniature swine model.

AU Smith D M; Stribley J A; Lieberman R P; Sharp J G

CS Department of Pathology, University of Nebraska Medical Center, Omaha.

SO JOURNAL OF CLINICAL APHERESIS, (1992) 7 (2) 49-57.
Journal code: 8216305. ISSN: 0733-2459.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199212

ED Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921222

AB A large animal model is needed to evaluate new apheresis technologies. These technologies include novel methods of harvesting the blood mononuclear cell population which contains the hematopoietic stem cells needed to restore hematopoiesis in recipients of hematopoietically lethal

therapy and the use of cytokines to provide a safe and predictable method of manipulating these circulating hematopoietic stem cells. We describe the methods used to collect mononuclear cells by leukapheresis from Yucatan miniature swine. These animals are of sufficient size to tolerate the procedures and have many physiologic and hematologic similarities to man. They are of good temperament and are easily trained. Long-term venous access was obtained using single lumen silicone rubber catheters placed in the inferior vena cava. The animals were apheresed while fully awake using a Haemonetics Model V50 machine and a modified lymphocyte collection protocol. The procedure was highly efficient for the collection of mononuclear cells and a 10 pass procedure yielded a product which contained 19.7 x 10(9) mononuclear cells, 10.7 x 10(9) granulocytes, and 17 ml of erythrocytes in a volume of approximately 100 ml. This product can be cryopreserved and used for subsequent transplantation. The content of four apheresis procedures provides hematopoietic reconstitution of lethally irradiated swine on a time scale equivalent to transplantation of optimal numbers of bone marrow cells.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Bone Marrow Cells
Catheterization, Central Venous
*Leukapheresis
***Leukocytes, Mononuclear: TR, transplantation**
*Models, Biological
Monitoring, Physiologic
Specimen Handling: MT, methods
Swine
Swine, Miniature
Vena Cava, Inferior
Whole-Body Irradiation

L148 ANSWER 6 OF 7 MEDLINE
AN **92003969** MEDLINE
DN **92003969** PubMed ID: **1912590**
TI Late failure of autologous marrow grafts in lethally irradiated dogs given anti-class II monoclonal antibody.
AU Greinix H T; Ladiges W C; Graham T C; Maslan S; Raff R F; Sandmaier B M; Appelbaum F R; Schuening F G; Deeg H J; Storb R
CS Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA 98104.
NC CA01483 (NCI)
CA15704 (NCI)
CA18221 (NCI)
+
SO BLOOD, (1991 Oct 15) 78 (8) 2131-8.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199111
ED Entered STN: 19920124
Last Updated on STN: 19970203
Entered Medline: 19911114
AB We established a model of canine marrow autografts after 9.2 Gy total body irradiation (TBI) to study the role of class II antigens in hematopoietic stem cell growth and differentiation. Twenty dogs were given 9.2 Gy TBI, marrow, and intravenous (IV) murine anti-class II monoclonal antibody (MoAb). Infusion of 0.6 mg/kg/d of MoAb H81.98.21, an IgG2a reactive with HLA-DR, on days 0 to 4 after TBI did not prevent initial engraftment, but dogs died with late graft failure. MoAb B1F6, an IgG2a reactive with HLA-DR + DP, had no adverse effect on engraftment, although both MoAbs detect antigens on stem cells. The critical time for the effect of MoAbs is the first 4 days after transplantation. Our findings argue against

several pathogenetic mechanisms, including removal of MoAb-coated stem cells by the reticuloendothelial system (RES), canine complement-mediated cytotoxic effects on stem cells, antibody-dependent cellular cytotoxicity, and inactivation of MoAb-coated cells by dog anti-mouse antibody. To distinguish between MoAb-induced damage to microenvironment (ME)/accessory cells (AC) and late graft failure from a lack of pluripotent stem cells, three dogs were given TBI, a marrow autograft, and MoAb H81.98.21 on days 0 to 4; one, given thoracic duct cells on day 6, developed graft failure; the other two, given marrow depleted of AC by L-leucyl L-leucine o-methyl ester (Leu-Leu-OMe), had sustained grafts. Findings support the notion that originally transplanted pluripotent stem cells are no longer present on day 6 and that the ME is functional and able to support newly injected stem cells.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antibodies, Monoclonal: AD, administration & dosage
***Bone Marrow Transplantation: IM, immunology**
Combined Modality Therapy
Dogs
*Graft Rejection: RE, radiation effects
Hematopoietic Stem Cells
*Histocompatibility Antigens Class II: IM, immunology
Immunotherapy, Adoptive
Injections, Intravenous
Transplantation, Autologous
***Whole-Body Irradiation**

CN 0 (Antibodies, Monoclonal); 0 (Histocompatibility Antigens Class II)

L148 ANSWER 7 OF 7 MEDLINE
AN **83204692** MEDLINE
DN **83204692** PubMed ID: **6133548**
TI Transplantation of bone marrow fibroblastoid stromal cells in mice via the intravenous route.
AU Piersma A H; Ploemacher R E; Brockbank K G
SO BRITISH JOURNAL OF HAEMATOLOGY, (1983 Jun) 54 (2) 285-90.
Journal code: 0372544. ISSN: 0007-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198307
ED Entered STN: 19900319
Last Updated on STN: 19950206
Entered Medline: 19830715

AB Kinetics of fibroblastic colony-forming cells (CFU-F) were studied in mouse bone marrow after lethal total body irradiation and intravenous bone marrow transplantation. After an initial decrease, CFU-F numbers recovered, and plateaued 5 weeks post-treatment at 10% of normal values. Using chromosome-marked donor bone marrow cells we found that 1 day after transplantation 72% of donor CFU-F had reached the recipient's bone marrow, indicating a highly specific lodgment of CFU-F. Three months after transplantation donor CFU-F were still detectable and comprised about half of the femoral CFU-F population. It is concluded that CFU-F, a component of the haemopoietic microenvironment, are transplantable via the intravenous route.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
***Bone Marrow Transplantation**
Cells, Cultured
Colony-Forming Units Assay
Fibroblasts: TR, transplantation
Genetic Markers
Hematopoiesis
Hematopoietic Stem Cell Transplantation

Injections, Intravenous
Mice
Mice, Inbred Strains
Time Factors
Whole-Body Irradiation
CN 0 (Genetic Markers)

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E JP97-52930/AP,PRN
L1 1 S E4
E JP97-155015/AP,PRN
L2 1 S E3
E JP97-346737/AP,PRN
L3 1 S L1,L2
E IKEHARA S/AU
L4 140 S E3,E10,E11
E SUGIURA K/AU
L5 107 S E3,E4,E54
E JIN T/AU
L6 72 S E3-E8
E JIN TIENAN/AU
L7 7 S E3
E MORITA H/AU
L8 317 S E3-E5,E13
E SOGO S/AU
L9 21 S E3,E9
E YAMANISHI K/AU
L10 59 S E3,E10
E ADACHI M/AU
L11 328 S E3,E27
E SUSUMU/AU
E KIKUYA/AU
E TIENAN/AU
E HARUO/AU
E SHINJI/AU
E KAZUYA/AU
E MASAKAZU/AU
L12 2 S E3
E OTSUKA/PA,CS
L13 4652 S E3,E4
L14 4653 S OTSUKA?/PA,CS
E TRANSPLANT/CT
L15 494 S E3
L16 28158 S E5
E E4+ALL
E E2+ALL
L17 7339 S E7-E12
L18 28226 S E6+NT
E E38+ALL
L19 4717 S E2+NT
E E5+ALL
L20 13859 S E5+NT
E E10+ALL
L21 11905 S E2+NT
E E6+ALL
L22 5970 S E3

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L23       55691 S L15-L22
                E TELEROGEN
                E TOLEROGEN
L24         235 S L23 AND E3
L25         515 S L23 AND E4-E14
L26         648 S L24,L25
L27          22 S L26 AND HEMATOPO?
                E HEMATOPO/CT
L28           1 S L26 AND E4-E27
                E E4+ALL
L29           1 S L26 AND E4,E3+NT
                E E10+ALL
L30          13 S L26 AND E5+NT
                E E29+ALL
                E E12+ALL
L31          11 S L26 AND E2,E1+NT
                E E21+ALL
L32           1 S L26 AND E7,E8,E6+NT
                E E19+ALL
                E E13+ALL
L33           0 S L26 AND E5,E6,E4+NT
L34          32 S L27-L32
                E BONE MARROW/CT
                E E3+ALL
L35          27 S L26 AND E16+NT
L36          91 S L26 AND BONE MARROW
L37         108 S L34-L36
L38          16 S L37 AND ?RADIAT?
L39           2 S L37 AND RADI?/SC,SX
L40          18 S L38,L39
L41          59 S L4-L14 AND L23
L42           1 S L41 AND L26
L43           8 S L41 AND ?RADI?
L44           2 S L41 AND RADI?/SC,SX
L45           8 S L43,L44
L46          10 S L41 AND IRRAD?
L47          12 S L45,L46
L48          10 S L47 AND BONE MARROW
L49           2 S L47 NOT L48
L50           1 S L49 NOT HBNO/TI
                SEL DN AN 1 2 4-10  L48
L51           9 S E1-E27 AND L48
L52          10 S L50,L51
L53          11 S L3,L52
L54           4 S L26 AND RADI?/SC,SX
L55          57 S L26 AND ?RADI?
L56          36 S L26 AND IRRAD?
L57          58 S L54-L56
                E RADIATION/CT
                E E3+ALL
L58           6 S L26 AND E2,E3,E1+NT
L59           3 S L26 AND (E142+NT OR E146+NT)
                E E150+ALL
L60           3 S L26 AND E6+NT
L61          58 S L57-L60
L62          21 S L61 AND L37
L63          19 S L61 AND ?BONE MARROW?
L64           0 S L61 AND ?BONEMARROW?
L65          21 S L62,L63
L66          32 S L53,L65
L67          37 S L61 NOT L66
L68          32 S L66 AND L1-L67
L69          27 S L68 AND (PD<=1998 OR PRD<=1998 OR AD<=1998)
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L70           5 S L68 NOT L69
L71          32 S L69,L70

     FILE 'HCAPLUS' ENTERED AT 16:42:42 ON 17 MAR 2003

     FILE 'WPIX' ENTERED AT 16:42:51 ON 17 MAR 2003
                E WO98-JP909/AP,PRN
L72            1 S E3
                E JP97-52930/AP,PRN
L73            1 S E4
                E JP97-155015/AP,PRN
L74            1 S E3,E4
                E JP97-346737/AP,PRN
L75            1 S E3,E4
L76            1 S L72-L75
                E OTSUKA/PA
L77         4625 S E3
L78         4626 S OTSUKA?/PA
                E SAKA/PACO
L79         7574 S E3-E10
L80        10126 S L77-L79
                E IKEHARA S/AU
L81            7 S E3
                E SUGIURA K/AU
L82          125 S E3,E4
                E JIN T/AU
L83           98 S E3-E12
                E MORITA H/AU
L84          313 S E3,E4
                E SOGO S/AU
L85           23 S E3
                E YAMANISHI K/AU
L86           45 S E3,E4
                E ADACHI M/AU
L87          292 S E3
L88          894 S L81-L87
L89         3194 S (B14-G02C OR C14-G02C)/MC
L90         1496 S (B12-D02B OR C12-D02B)/MC
L91         4122 S (B14-G02 OR C14-G02)/MC
L92         8528 S L89-L91
L93         1403 S A61P037-06/IC,ICM,ICS,ICA,ICI OR A61P037:06/ICI
L94         9150 S L92,L93
L95           10 S L94 AND A61N005/IC,ICM,ICS,ICA,ICI
L96            0 S L94 AND K08-H01/MC
L97            4 S L94 AND S05-A03?/MC
L98          185 S L94 AND IRRAD?/BIX
L99         1407 S L94 AND ?RADI?/BIX
L100          68 S L94 AND A61K035-28/IC,ICM,ICS,ICA,ICI
L101         719 S L94 AND (?BONEMARROW? OR ?BONE MARROW?)/BIX
L102           3 S L95-L99 AND (V642/M0,M1,M2,M3,M4,M5,M6 OR A61K035:28/ICI)
L103           6 S L95-L99 AND (B04-B04E OR C04-B04E)/MC
L104         204 S L95-L99 AND L100,L101
L105         209 S L102,L103,L104
                E TOLEROGEN
L106           5 S E3-E10/BIX AND L105
L107          55 S A61K039/IC,ICM,ICS AND L105
L108          57 S L106,L107
L109          24 S L108 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
                SEL DN AN 1-3 9 10 12 14 16 18 19 21 23
L110          12 S L109 AND E1-E25
L111          12 S L76,L110
L112          25 S L88,L80 AND L94
L113           5 S L112 AND L95-L100
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                SEL DN AN 2 3
L114            2 S E26-E29 AND L113
L115            2 S L112  AND L105-L108
L116            2 S L114,L115
L117           20 S L112 NOT L113
L118           13 S L116,L111 AND L72-L117

      FILE 'WPIX' ENTERED AT 17:28:20 ON 17 MAR 2003

      FILE 'MEDLINE' ENTERED AT 17:28:37 ON 17 MAR 2003
                E TRANSPLANT/CT
                E E11+ALL
L119       259691 S E3+NT
L120        67612 S E51
L121       170750 S E46+NT OR E48+NT OR E49+NT
L122       261139 S L119-L121
                E IRRADIATION/CT
                E E17+ALL
                E E2+ALL
L123         2409 S L122 AND E6+NT
                E BONE MARROW/CT
                E E5+ALL
L124          315 S L123 AND E6+NT
                E HEMATOP/CT
L125          126 S L123 AND E6+NT
                E E6+ALL
                E HEMATOPO/CT
L126          121 S L123 AND E22+NT
L127           25 S L123 AND E63+NT
L128          368 S L123 AND E77+NT
L129          242 S L123 AND E96+NT
L130           44 S L126 AND E120+NT
                E E62+ALL
L131          242 S L123 AND E2+NT
L132          673 S L124-L131
                E TOLEROGEN
L133            0 S L132 AND E3-E21
L134          165 S L132 AND (ANTIGEN? OR ANTIBOD?)
L135            0 S L132 AND (HEPATIC OR LIVER)(L)(VEIN OR VENOUS)(L)PORTAL
                E VENOUS ADMINISTRATION/CT
                E E11+ALL
                E E2+ALL
                E E5+ALL
L136       104022 S E5+NT
L137            2 S L132 AND L136
                E CATHETER/CT
                E E122+ALL
                E CATHETERS/CT
                E E6+ALL
L138         9503 S E3+NT
L139            1 S L132 AND L138
L140            2 S L137,L139
L141        10353 S (HEPATIC OR LIVER)(S)PORTAL(S)(VEIN OR VENOUS)
L142         4271 S (HEPATIC OR LIVER)(S)PORTAL(S)(VEIN OR VENOUS)(S)(INFUS? OR A
                E DRUG ADMINISTRATION/CT
                E E5+ALL
L143        88536 S E28,E36,E48
L144            9 S L143 AND L132
                SEL DN AN 2 3 4 6 8 9
L145            6 S L144 AND E1-E18
                E PORTAL VEIN/CT
                E E3+AL
                E E3+ALL
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L146 11527 S E6+NT
L147 1 S L132 AND L146
L148 7 S L140,L145,L147

FILE 'MEDLINE' ENTERED AT 17:42:29 ON 17 MAR 2003